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Supporting information

New Synthesis of Tetraoxaspirododekane-diamines and Tetraoxazaspirobicycloalkanes

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A. General Information

General Remarks. All reactions were performed at room temperature in air in round-bottom flasks equipped with a magnetic stir bar. The NMR spectra were recorded on a Bruker Avance 500 spectrometer at 500.17 MHz for ^{1}H and 125.78 MHz for ^{13}C according to standard Bruker procedures. CDCl3 was used as the solvent, and tetramethylsilane, as the internal standard. The mixing time for the NOESY experiments was 0.3 sec. Mass spectra were recorded on a Bruker Autoflex III MALDI TOF/TOF instrument with α-cyano-4-hydroxycinnamic acid as a matrix. Samples were prepared by the dried droplet method. The C, H, and N were quantified by a Carlo Erba 1108 analyzer. The oxygen content was determined on a Carlo Erba 1108 analyzer. The progress of reactions was monitored by TLC on Sorbfil (PTSKh-AF-A) plates, with a 5:1

hexane : EtOAc mixture as the eluent and visualization with I_2 vapor. For column chromatography, silica gel MACHEREY-NAGEL (0.063-0.2 mm) was used.

All calculations were carried out using a program Gaussian 09. Geometric parameter optimization, vibrational frequency analysis, and calculation of entropy and thermodynamic corrections to the total energy of the compounds were carried out on the B3LYP functional[1] using the 6-31G(d,p) basis set. No limitation was imposed on the changes in the geometric parameters of the subsystems studied. Thermodynamic parameters were determined at 298 K. The minima were confirmed through the calculation of the force constant (Hessian) matrix and the analysis of the resulting frequencies. All minima were verified to have no negative frequencies. Visualization of quantum chemical data was carried out with the programs ChemCraft.[1]

The X-ray diffraction measurements for compounds **4a, 4b, 4d, 4e, 12b** were performed on an XCalibur Gemini Eos automated four-circle diffractometer (graphite monochromator, MoKα radiation, $\lambda = 0.71073$ Å, ω-scan mode, $2\theta max = 62°$) at ambient temperature (293–298 K). Collected data were processed using the program CrysAlisPro.[2] Structures determinations were carried out with the OLEX2 program.[3] The structures were solved by direct methods and refined by the full-matrix least-squares method in the anisotropic approximation for non-hydrogen atoms. All hydrogen atoms are generated using the proper HFIX command and refined isotropically using the riding model. The calculations were performed using the SHELX program package.[4] The molecular plots were drawn using Mercury.[5]

The synthesis of the *gem*-dihydroperoxides **1, 6-10** was as reported in the literature.[6] THF was freshly distilled over $LiAlH_4$. Glyoxal was used as aqueous solution (40%).

Cell culturing. Human cancer cell line HeLa was obtained from the HPA Culture Collections (UK). Cells (Jurkat, K562, U937, Fibroblasts) were purchased from Russian Cell Culture Collection (Institute of Cytology of the Russian Academy of Sciences) and cultured according to standard protocols and sterile technique. The cell lines were shown to be free of viral contamination and mycoplasma. Cells were maintained in RPMI 1640 (Jurkat, K562, U937, Fibroplast) (Gibco) supplemented with 4 μM glutamine, 10% FBS (Sigma) and 100 units/ml penicillin-streptomycin (Sigma). All types of cells were grown in an atmosphere of 5% CO2 at 37 °C. The cells were subcultured at 2–3 days intervals. Cells were then seeded in 24 well plates at 5×10^4 cells per well and incubated overnight.

Jurkat, K562, U937, Fibroplast cells were subcultured at 2-day intervals with a seeding density of 1×10^5 cells per 24 well plates in RPMI with 10% FBS.

Cytotoxicity assay. Viability (Live/dead) assessment was performed by staining cells with 7-AAD (7-Aminoactinomycin D) (Biolegend). After treatment cells were harvested, washed 1-2 times with phosphate-buffered saline (PBS) and centrifuged at 400 g for 5 min. Cell pellets were resuspended in 200 μL of flow cytometry staining buffer (PBS without Ca2+ and Mg2+, 2.5% FBS) and stained with 5 μL of 7-AAD staining solution for 15 min at room temperature in the dark. Samples were acquired on NovoCyte TM 2000 Flow Cytometry System (ACEA) equipped with 488 nm argon laser. Detection of 7-AAD emission was collected through a 675/30 nm filter in the FL4 channel.

Cyclocondensation reactions of primary arylamines with gem-dihydroperoxides and α,ω-dialdehydes (glyoxal, pentanedial) catalyzed by $Sm(NO_3)_3{\cdot}6H_2O$.

General procedure: A Schlenk vessel mounted on a magnetic stirrer was charged at ~20°C with tetrahydrofuran (5 ml), *α,ω-dialdehydes (glyoxal, pentanedial)* (10 mmol), and specified gem-dihydroperoxides (10 mmol).[6] Then $Sm(NO_3)_2{\cdot}6H_2O$ (0.062 g, 5 mol. % relative to 1,1'-peroxybis(1-hydroperoxycycloalkane)) was added. The reaction mixture was stirred at ~20°C for 1 h, after which *primary arylamines* (20 mmol) was added, and the reaction mixture was stirred at ~20°C for 6 h more. After completion of the reaction H_2O (5 ml) and CH_2Cl_2 (5 ml) were added. The organic layer was separated, dried (anhydrous $MgSO_4$) and concentrated to isolate products stable during storage at room temperature. Products of the reaction were purified by column chromatography on SiO_2 using 10 : 1 PE : Et_2O as the eluent. The progress of reactions was monitored by TLC, with a 5 : 1 hexane : EtOAc mixture as the eluent, visualization was performed with I_2 vapor.

N^9,N^{10}-bis(4-chlorophenyl)-7,8,11,12-tetraoxaspiro[5.6]dodecane-9,10-diamine 4a

White crystals; 0.37 g (87% yield), R_f 0.77 (PE/Et_2O = 10/1), mp 120-122°C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.28-1.48 (m, 2H, CH_2), 1.69 (br.s, 4H, $2CH_2$), 1.77-1.89 (m, 4H, $2CH_2$), 5.57 (br.s, 2H, 2CH), 7.13-7.15 (m, 4H, CH), 7.18-7.21 (m, 4H, CH). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.6 (*conformer **A***), 22.8 (*conformers **B**+**C***), 25.1, 31.2 (*conformer **A***), 31.4 (*conformers **B**+**C***), 85.1, 115.8, 116.3, 124.7, 128.6, 145.1. MALDI TOF/TOF, m/z: 424 $[M-H]^+$. Anal.calcd. For $C_{20}H_{22}Cl_2N_2O_4$: C, 56.48; H, 5.21; N, 6.59%. Found: C, 56.46; H, 5.19; N, 6.57%.

N^9,N^{10}-bis(2-fluorophenyl)-7,8,11,12-tetraoxaspiro[5.6]dodecane-9,10-diamine 4b

White crystals; 0.33 g (85% yield), R_f 0.75 (PE/Et_2O = 10/1), mp 134-136°C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.28-1.36 (m, 2H, CH_2), 1.43-1.45 (m, 4H, $2CH_2$), 1.60-1.61 (m, 4H, $2CH_2$), 5.70 (br.s, 2H, 2CH), 6.87-6.89 (m, 2H, CH), 7.02-7.10 (m, 4H, CH), 7.18-7.24 (m, 2H, CH). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.6, 25.1, 29.7, 89.7, 111.5, 114.5,115.2 (*J*=19), 120.3 (*J*=17), 124.7, 142.5, 164.1 (*J*=192). MALDI TOF/TOF, m/z: 391 $[M-H]^+$. Anal.calcd. For $C_{20}H_{22}F_2N_2O_4$: C, 61.22; H, 5.65; N, 7.14%. Found: C, 61.20; H, 5.63; N, 7.11%.

N^9,N^{10}-bis(3-fluorophenyl)-7,8,11,12-tetraoxaspiro[5.6]dodecane-9,10-diamine 4c

White crystals; 0.34 g (85% yield), R_f 0.78 (PE/Et_2O = 10/1), mp 138-140°C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.30-1.46 (m, 2H, CH_2), 1.61 (br.s, 4H, $2CH_2$), 1.77-1.84 (m, 4H, $2CH_2$), 5.62 (br.s, 2H, 2CH), 6.58-6.68 (m, 6H, CH), 7.18-7.25 (m, 2H, CH). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.6 (*conformer **A***), 22.7 (*conformers **B**+**C***), 25.0 (*conformer **A***), 25.2 (*conformers **B**+**C***), 31.2 (*conformer **A***), 31.6 (*conformers **B**+**C***), 88.2, 102.5 (*J*=7),111.1, 112.1, 107.2 (*J*=17), 130.7 (*J*=8), 145.6, 163.8 (*J*=195). MALDI TOF/TOF, m/z: 391 $[M-H]^+$. Anal.calcd. For $C_{20}H_{22}F_2N_2O_4$: C, 61.22; H, 5.65; N, 7.14%. Found: C, 61.19; H, 5.63; N, 7.12%.

N^9,N^{10}-bis(4-fluorophenyl)-7,8,11,12-tetraoxaspiro[5.6]dodecane-9,10-diamine 4d

White crystals; 0.35 g (88% yield), R_f 0.74 (PE/Et_2O = 10/1), mp 128-130°C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.28-1.45(m, 2H, CH_2), 1.61 (br.s, 4H, $2CH_2$), 1.77-1.89 (m, 4H, $2CH_2$), 5.57 (br.s, 2H, 2CH), 6.80-6.88 (m, 4H, CH), 6.96-7.01 (m, 4H, CH). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.6, 25.1, 31.2 (*conformer **A***), 31.4 (*conformers **B**+**C***), 89.4, 111.9, 116.0 (*J*=18), 121.6, 139.9, 157.7 (*J*=190). MALDI TOF/TOF, m/z: 391 $[M-H]^+$. Anal.calcd. For $C_{20}H_{22}F_2N_2O_4$: C, 61.22; H, 5.65; N, 7.14%. Found: C, 61.20; H, 5.62; N, 7.12%.

N^9,N^{10}-bis(4-bromophenyl)-7,8,11,12-tetraoxaspiro[5.6]dodecane-9,10-diamine 4e

White crystals; 0.43 g (90% yield), R_f 0.72 (PE/Et_2O = 10/1), mp 122-124°C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.28-1.48 (m, 2H, CH_2), 1.63 (br.s, 4H, $2CH_2$), 1.77-1.85 (m, 4H, $2CH_2$), 5.56 (br.s, 2H, 2CH), 6.73-6.75 (m, 4H, CH), 7.34-7.35 (m, 4H, CH). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.6, 24.9, 30.7 (*conformer **A***), 31.3 (*conformers **B**+**C***), 89.3, 106.4, 112.2, 116.0, 121.5, 132.2. MALDI TOF/TOF, m/z: 513 $[M-H]^+$.

Anal.calcd. For $C_{20}H_{22}Br_2N_2O_4$: C, 46.72; H, 4.31; N, 5.45%. Found: C, 46.70; H, 4.29; N, 5.43%.

11-(4-chlorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclopentane] 11a

Brown oil; 0.24 g (75% yield), R_f 0.79 (PE/Et_2O = 10/1). ^1H NMR (500.17 MHz, $CDCl_3$, 25 °C): δ = 1.54-1.59 (m, 1H, CH_a, *conformers* ***B***+***C***), 2.40-2.44 (m, 1H, CH_b, *conformers* ***B***+***C***), 2.13-2.19 (m, 2H, CH_2, *conformer* ***A***), 1.53-2.10 (m, 4H, $2CH_2$), 1.70-1.97 (m, 4H, $2CH_2$), 2.45-2.35 and 2.13-2.20 and 1.76-1.82 and 1.50-1.60 (m, 4H, $2CH_2$), 5.35-5.36 (m, 2H, 2CH, *conformer* ***B***), 5.65 (s, 2H, 2CH, *conformer* ***A***), 5.77 (s, 2H, 2CH, *conformer* ***C***), 6.77-6.87 (m, 2H, CH), 7.13-7.20 (m, 2H, CH). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 °C): δ = 14.2 (*conformer* ***A***), 16.0 (*conformers* ***B***+***C***), 23.2 (*conformer* ***A***), 24.3 (*conformers* ***B***+***C***), 24.6 (*conformer* ***A***), 26.4 (*conformer* ***A***), 27.1 (*conformers* ***B***+***C***), 33.5 (*conformers* ***B***+***C***), 33.7 (*conformer* ***A***), 34.0 (*conformers* ***B***+***C***), 34.2 (*conformer* ***A***), 88.2 (*conformer* ***B***), 88.9 (*conformer* ***A***), 89.1 (*conformer* ***C***), 113.4, 114.2 (*conformers* ***B***+***C***), 120.7 (*conformer* ***A***), 128.0, 129.2 (*conformer* ***A***), 140.2 (*conformer* ***B***+***C***), 159.7. MALDI TOF/TOF, m/z: 324 $[M-H]^+$. Anal.calcd. For $C_{16}H_{20}ClNO_4$: C, 58.99; H, 6.19; N, 4.30 %. Found: C, 58.97; H, 6.17; N, 4.27%.

11-(4-bromophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclopentane] 11e

Brown solid; 0.26 g (71% yield), R_f 0.77 (PE/Et_2O = 10/1), mp 110-112°C. ^1H NMR (500.17 MHz, $CDCl_3$, 25 °C): δ = 1.57-1.60 (m, 1H, CH_a, *conformers* ***B***+***C***), 2.43-2.47 (m, 1H, CH_b, *conformers* ***B***+***C***), 2.13-2.20 (m, 2H, CH_2, *conformer* ***A***), 1.57-2.11 (m, 4H, $2CH_2$), 1.70-1.97 (m, 4H, $2CH_2$), 2.47-2.39 and 2.13-2.20 and 1.74-1.80 and 1.52-1.60 (m, 4H, $2CH_2$), 5.27-5.28 (m, 2H, 2CH, *conformer* ***B***), 5.67 (s, 2H, 2CH, *conformer* ***A***), 5.81 (s, 2H, 2CH, *conformer* ***C***), 7.06-7.10 (m, 2H, CH), 7.35-7.39 (m, 2H, CH). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 °C): δ = 14.3 (*conformer* ***A***), 16.0 (*conformers* ***B***+***C***), 23.3 (*conformer* ***A***), 24.6 (*conformers* ***B***+***C***), 24.9 (*conformer* ***A***), 26.4 (*conformer* ***A***), 27.1 (*conformers* ***B***+***C***), 32.4 (*conformers* ***B***+***C***), 33.5 (*conformer* ***A***), 33.7 (*conformers* ***B***+***C***), 34.6 (*conformer* ***A***), 86.5 (*conformer* ***B***), 87.1 (*conformer* ***A***), 87.4 (*conformer* ***C***), 113.1, 119.7 (*conformers* ***B***+***C***), 120.50 (*conformer* ***A***), 124.5, 131.6 (*conformer* ***A***), 132.4 (*conformer* ***B***+***C***), 149.2. MALDI TOF/TOF, m/z: 369 $[M-H]^+$. Anal.calcd. For $C_{16}H_{20}BrNO_4$: C, 51.91; H, 5.45; N, 3.78%. Found: C, 51.89; H, 5.43; N, 3.76%.

11-(4-chlorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 12a

Orange oil; 0.27 g (80% yield), R_f 0.75 (PE/Et_2O = 10/1). ^1H NMR (500.17 MHz, $CDCl_3$, 25 ^oC): δ = 1.57-1.62 (m, 1H, CH_a, *conformers* ***B***+***C***), 2.11-2.20 (m, 1H, CH_b, *conformers* ***B***+***C***), 2.39-2.46 (m, 2H, CH_2, *conformer* ***A***), 1.44-1.62 (m, 4H, $2CH_2$), 1.44-1.50 (m, 4H, $2CH_2$), 1.78-1.87 and 1.97-2.00 (m, 4H, $2CH_2$), 1.31-1.34 and 2.20-2.24 (m, 4H, $2CH_2$), 5.37-5.38 (m, 2H, 2CH, *conformer* ***B***), 5.68 (s, 2H, 2CH, *conformer* ***A***), 5.84 (s, 2H, 2CH, *conformer* ***C***), 7.05-7.19 (m, 1H, CH), 7.21-7.22 (m, 1H, CH), 6.89-6.95 (m, 1H, CH), 7.17-7.19 (m, 1H, CH). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 ^oC): δ = 14.6 (*conformer* ***A***), 16.2 (*conformers* ***B***+***C***), 22.0 (*conformer* ***A***), 22.5 (*conformers* ***B***+***C***), 22.7 (*conformer* ***A***), 22.9 (*conformer* ***A***), 25.3 (*conformers* ***B***+***C***), 25.4 (*conformers* ***B***+***C***), 26.4 (*conformer* ***A***), 26.9 (*conformers* ***B***+***C***), 28.7 (*conformer* ***A***), 29.7 (*conformers* ***B***+***C***), 30.7 (*conformer* ***B***+***C***), 31.2 (*conformer* ***A***), 85.9 (*conformer* ***B***), 86.8 (*conformer* ***C***), 86.9 (*conformer* ***A***), 108.8 (*conformers* ***B***+***C***), 109.5 (*conformers* ***A***), 116.2 (*conformers* ***B***+***C***), 116.8 (*conformer* ***A***), 118.4 (*conformers* ***B***+***C***), 119.0 (*conformers* ***A***), 120.6 (*conformers* ***A***), 121.3 (*conformers* ***B***+***C***), 129.7 (*conformers* ***A***), 129.9 (*conformers* ***B***+***C***), 134.4 151.2. MALDI TOF/TOF, m/z: 338 $[M-H]^+$. Anal.calcd. For $C_{17}H_{22}ClNO_4$: C, 60.09; H, 6.53 N, 4.12%. Found: C, 60.07; H, 6.51 N, 4.10%.

11-(2-fluorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 12b

Brown crystals; 0.26g (83% yield), R_f 0.77 (PE/Et_2O = 10/1), mp 80-82^oC. ^1H NMR (500.17 MHz, $CDCl_3$, 25 ^oC): δ = 1.56-1.60 (m, 1H, CH_a), 2.14-2.24 (m, 1H, CH_{b},), 1.60-1.66 (m, 2H, CH_2), 1.54-1.59 (m, 2H, CH_2), 1.46-1.50 (m, 4H, $2CH_2$), 1.87-2.02 (m, 4H, $2CH_2$), 2.28-2.30 (m, 2H, CH_2), 5.15 (d, 2H, *J* = 10 Hz, 2CH, *conformer* ***B***), 5.34 (br.s, 2H, 2CH, *conformer* ***A***), 5.44-5.45 (m, 2H, 2CH, *conformer* ***C***), 6.93-7.12 (m, 3H, CH), 7.84-7.87 (m, 1H, CH). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 ^oC): δ = 14.9 (*conformer* ***A***), 16.4 (*conformers* ***B***+***C***), 22.0 (*conformer* ***A***), 22.6 (*conformers* ***B***+***C***), 22.9 (*conformer* ***B***+***C***), 22.9 (*conformer* ***A***), 25.4 (*conformers* ***B***+***C***), 25.5 (*conformers* ***B***+***C***), 26.1 (*conformer* ***A***), 30.8 (*conformers* ***B***+***C***), 31.6 (*conformer* ***A***), 88.9 (*conformer* ***B***), 89.3 (*conformer* ***A***), 89.5 (*conformer* ***C***), 108.7 (*conformers* ***B***+***C***), 115.9 (*J* = 17, *conformers* ***B***+***C***), 116.1 (*J* = 17 Hz, *conformers* ***A***), 123.6 (*J* = 6), 124.4, 124.8, 137.9 (*J* = 6), 156.3

(J = 193). MALDI TOF/TOF, m/z: 322 [M-H]$^+$. Anal.calcd. For $C_{17}H_{22}FNO_4$: C, 63.14; H, 6.86; N, 4.33%. Found: C, 63.12; H, 6.84; N, 4.30%.

11-(3-fluorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 12c

Brown oil; 0.24g (75% yield), R_f 0.81 (PE/Et_2O = 10/1). ^{1}H NMR (500.17 MHz, $CDCl_3$, 25 ^{o}C): δ = 1.31-1.46 (m, 4H, CH_2, $2CH_a$), 1.48-1.62 (m, 5H, $2CH_2$, CH_a), 1.72-1.99 (m, 4H, $2CH_2$), 2.14-2.19 (m, 1H, CH_b), 2.22-2.25 (m, 2H, CH_b), 5.37-5.39 (m, 2H, 2CH, *conformer **C***), 5.69 (br.s, 2H, 2CH, *conformer **A***), 5.85-5.86 (m, 2H, 2CH, *conformer **B***), 6.59-6.68 (m, 1H, CH), 6.89-6.98 (m, 2H, CH), 7.15-7.25 (m, 1H, CH). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 ^{o}C): δ = 14.2 (*conformer **B**+**C***), 14.6 (*conformer **A***), 21.0 (*conformers **B**+**C***), 22.0 (*conformer **A***), 22.5 (*conformer **B***), 22.7 (*conformer **A***), 22.8 (*conformer **C***), 25.0 (*conformer **C***), 25.3 (*conformer **B***), 25.4(*conformer **A***), 26.4 (*conformer **A***), 26.9 (*conformer **C***), 27.0 (*conformer **B***), 85.6 (*conformer **B***), 86.7 (*conformer **C***), 86.9 (*conformer **A***), 104.8 (J=17, *conformer **C***), 105.3 (J=20, *conformer **B***), 105.9 (J=20, *conformer **A***), 107.2 (J=17 *conformer **A***), 107.8 (J = 17, *conformers **B**+**C***), 108.8 (*conformers **B**+**C***), 109.5 (*conformer **A***), 113.3 (*conformers **B**+**C***), 114.0 (*conformer **A***), 129.7 (J = 8, *conformers **A***), 129.9 (J = 7, *conformer **B***), 130.4 (J = 8, *conformer **C***), 151.3 (J = 8, *conformers **B**+**C***), 151.8 (J=8, *conformer **A***), 163.3 (J = 194). MALDI TOF/TOF, m/z: 322 [M-H]$^+$. Anal.calcd. For $C_{17}H_{22}FNO_4$: C, 63.14; H, 6.86; N, 4.33%. Found: C, 63.11; H, 6.85; N, 4.32%.

11-(2-chlorophenyl)-4'-methyl-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 13f

Orange oil; 0.27g (78% yield), R_f 0.76 (PE/Et_2O = 10/1). ^{1}H NMR (500.17 MHz, $CDCl_3$, 25 ^{o}C): δ = 0.97 (d, 3H, J = 10 Hz, CH_3, *conformer **A***), 1.04 (d, 3H, J = 10 Hz, CH_3, *conformer **B**+**C***), 1.58-1.59 and 2.21-2.28 (m, 2H, CH_2), 1.89-1.92 and 2.14-2.19 (m, 4H, $2CH_2$), 1.59-1.61 and 3.09-3.11 (m, 4H, CH_2), 1.23-1.73 (m, 4H, $2CH_2$), 1.98-2.03 (m, 1H, CH), 5.03-5.52 (m, 2H, 2CH), 6.69-6.78 (m, 2H, 2CH), 6.97-7.40 (m, 2H, 2CH). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 ^{o}C): δ = 14.2 (*conformer **C***), 15.0 (*conformers **A***), 16.6 (*conformer **B***), 21.6 (*conformer **A***), 21.0 (*conformers **B**+**C***), 25.9 and 26.0 and 26.7 (*conformers **A**+**B**+**C***), 30.9 and 31.2 (*conformer **B**+**C***), 31.0 (*conformers **A***), 31.4 (*conformers **B**+**C***), 31.5 (*conformer **A***), 31.7 and 31.9 (*conformers **B**+**C***), 31.7 (*conformer **A***), 34.8, 89.7 (*conformer **A***), 89.6 and 89.8 and 89.9 (*conformer **A**+**B**+**C***), 109.6, 113.7 (*conformers* ***B***+***C***), 115.9 (*conformers* ***A***), 119.0 (*conformer* ***A***), 119.3 and 119.4 (*conformers* ***B***+***C***), 127.4 and 127.6 and 127.8 (*conformers* ***B***+***C***), 127.6 (*conformers* ***A***), 129.2 (*conformers* ***B***+***C***), 129.4 (*conformers* ***A***), 130.2 (*conformers* ***B***+***C***), 130.5 (*conformer* ***A***), 143.0 (*conformer* ***B***+***C***), 147.1 (*conformer* ***A***),. MALDI TOF/TOF, m/z: 322 $[M-H]^+$. Anal.calcd. For $C_{18}H_{24}ClNO_4$: C, 61.10; H, 6.84; N, 3.96%. Found: C, 61.08; H, 6.82; N, 3.94%.

11-(2-chlorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclooctane] 14a

Orange oil; 0.26g (70% yield), R_f 0.77 (PE/Et_2O = 10/1). ^{1}H NMR (500.17 MHz, $CDCl_3$, 25 ^{o}C): δ = 1.56-1.59 (m, 1H, CH_a), 2.14-2.15 (m, 1H, CH_b), 1.63-1.67 and 1.51-1.53 (m, 4H, 2CH_2), 2.38-2.40 (m, 2H, 2CH_2), 2.17-2.24 and 1.95-2.00 and 1.77-1.87 (m, 6H, 3CH_2), 1.42-1.44 and 1.63-1.67 and 1.80-1.85 (m, 4H, 2CH_2), 5.67 (s, 2H, 2CH, *conformer* ***A***), 5.80 (s, 2H, 2CH, *conformer* ***B***+***C***), 7.01-7.03 (m, 2H, 2CH, *conformer* ***A***), 7.10-7.15 (m, 2H, 2CH, *conformer* ***B***+***C***), 6.96-6.97 (m, 2H, 2CH, *conformer* ***B***+***C***), 7.19-7.27 (m, 2H, 2CH, *conformer* ***A***). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 ^{o}C): δ = 14.6 (*conformer* ***A***), 16.3 (*conformer* ***B***+***C***), 22.0 (*conformers* ***B***+***C***), 22.3 (*conformer* ***A***), 22.1, 26.4 (*conformer* ***A***), 26.6 (*conformer* ***B***+***C***), 31.2 (*conformer* ***A***), 31.4 (*conformer* ***B***+***C***), 86.0 (*conformer* ***B***+***C***), 86.9 (*conformer* ***A***), 111.1, 119.0 (*conformer* ***A***), 119.8 (*conformer* ***B***+***C***), 124.5, 128.7 (*conformers* ***A***), 129.0 (*conformers* ***B***+***C***), 144.8. MALDI TOF/TOF, m/z: 366 $[M-H]^+$. Anal.calcd. For $C_{19}H_{26}ClNO_4$: C, 62.04; H, 7.12; N, 3.81%. Found: C, 62.02; H, 7.10; N, 3.79%.

11-(2-chlorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclooctane] 14g

Orange solid; 0.27g (74% yield), R_f 0.74 (PE/Et_2O = 10/1), mp 98-100^{o}C. ^{1}H NMR (500.17 MHz, $CDCl_3$, 25 ^{o}C): δ = 1.46-1.51 (m, 1H, CH_a), 2.09-2.19 (m, 1H, CH_b), 1.38-1.69 (m, 4H, 2CH_2), 2.34-2.36 and 1.38-1.50 (m, 2H, 2CH_2), 1.29-1.84 (m, 6H, 3CH_2), 1.34-1.40 (m, 4H, 2CH_2), 5.61 (s, 2H, 2CH, *conformer* ***A***), 5.75 (s, 2H, 2CH, *conformer* ***B***+***C***), 6.45-6.47 (m, 1H, CH), 6.58-6.59 (m, 1H, CH), 6.62-6.63 (m, 1H, CH), 6.95-7.19 (m, H, CH). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 ^{o}C): δ = 14.2 (*conformer* ***A***), 16.1 (*conformer* ***B***+***C***), 22.0 (*conformers* ***A***), 22.3 (*conformer* ***B***+***C***), 24.7 (*conformer* ***A***), 25.1 (*conformer* ***B***+***C***), 25.7, 31.0 (*conformer* ***B***+***C***), 31.4 (*conformers* ***A***), 85.8 (*conformer* ***B***), 86.7 (*conformer* ***C***), 86.7 (*conformer* ***A***), 113.3, 112.5 (*conformer* ***A***), 113.2 (*conformer*

B+***C***), 114.7, 117.9 (*conformers* ***A***), 118.2 (*conformers* ***B***+***C***), 129.7 (*conformers* ***B***+***C***), 130.3 (*conformers* ***A***), 134.3 (*conformers* ***B***+***C***), 134.6 (*conformers* ***A***), 147.4 (*conformers* ***B***+***C***), 148.1 (*conformers* ***A***). MALDI TOF/TOF, m/z: 366 $[M-H]^+$. Anal.calcd. For $C_{19}H_{26}ClNO_4$: C, 62.04; H, 7.12; N, 3.81%. Found: C, 62.01; H, 7.09; N, 3.79%.

11-(2-chlorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclododecane] 15a

Orange crystal; 0.33g (79% yield), R_f 0.78 (PE/Et_2O = 10/1), mp 82-84°C . ^{1}H NMR (500.17 MHz, $CDCl_3$, 25 °C): δ = 1.27-1.36 (m, 12H, 6CH_2), 1.70-1.75 (m, 2H, CH_2), 1.27-1.98 (m, 4H, 2CH_2), 2.15-2.20 and 1.98-2.20 (m, 4H, 2CH_2), 2.15-2.41 (m, 2H, CH_2), 5.35-5.36 (m, 2H, 2CH, *conformer* ***B***), 5.66 (s, 2H, 2CH, *conformer* ***A***), 5.82 (s, 2H, 2CH, *conformer* ***C***), 7.03-7.08 (m, 1H, CH), 7.15-7.21 (m, 2H, CH), 6.87-6.94 (m, 1H, CH). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 °C): δ = 14.2 (*conformer* ***A***), 16.1 (*conformer* ***B***+***C***), 22.0 (*conformers* ***A***), 22.3 (*conformer* ***B***+***C***), 24.7 (*conformer* ***A***), 25.1 (*conformer* ***B***+***C***), 25.7, 31.0 (*conformer* ***B***+***C***), 31.4 (*conformers* ***A***), 85.8 (*conformer* ***B***), 86.7 (*conformer* ***C***), 86.7 (*conformer* ***A***), 113.3, 112.5 (*conformer* ***A***), 113.2 (*conformer* ***B***+***C***), 114.7, 117.9 (*conformers* ***A***), 118.2 (*conformers* ***B***+***C***), 129.7 (*conformers* ***B***+***C***), 130.3 (*conformers* ***A***), 134.3 (*conformers* ***B***+***C***), 134.6 (*conformers* ***A***), 147.4 (*conformers* ***B***+***C***), 148.1 (*conformers* ***A***). MALDI TOF/TOF, m/z: 366 $[M-H]^+$. Anal.calcd. For $C_{23}H_{34}ClNO_4$: C, 65.16; H, 8.08; N, 3.30%. Found: C, 65.12; H, 8.06; N, 3.28%.

11'-(3-chlorophenyl)-2',3',5',6'-tetraoxa-11'-azaspiro[adamantane-2,4'-bicyclo[5.3.1]undecane] 16g

Brown oil; 0.28g (72% yield), R_f 0.80 (PE/Et_2O = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.66-1.74 (m, 2H, CH_2-Ad), 1.77 (m, 1H, CH-Ad, *conformer* ***A***), 1.82-1.86 (m, 8H, CH_2-Ad), 1.95-2.01 (m, 4H, CH_2-Ad, *conformer* ***A***), 2.04-2.06 (m, 4H, CH_2-Ad), 2.10-2.17 (m, 4H, 2CH_2), 2.19-2.28 (m, 2H, CH_2), 2.31 (br.s, 2H, CH_2-Ad), 2.39 (br.s, 1H, CH_2-Ad, *conformer* ***A***), 5.48-5.49 (m, 2H, 2CH, *conformer* ***B***), 5.68 (s, 2H, 2CH, *conformer* ***A***), 5.81 (s, 2H, 2CH, *conformer* ***C***), 6.77-6.84 (m, 1H, CH), 6.89-6.95 (m, 1H, CH), 7.02-7.13 (m, 1H, CH), 7.15-7.23(m, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.6 (*conformer* ***A***), 16.3 (*conformer* ***B***+***C***), 26.5, 27.1 (*conformer* ***B***+***C***), 27.2 (*conformer* ***A***), 30.3, 33.1 (*conformer* ***A***), 33.6 (*conformer* ***B***+***C***), 34.2 (*conformers* ***B***+***C***), 34.4 (*conformer **A***), 37.3 (*conformer **B**+**C***), 37.4 (*conformer **A***), 84.8 (*conformer **B***), 86.1 (*conformer **C***), 86.9 (*conformer **A***), 110.9 (*conformer **B***), 111.5 (*conformer **A**)*, 112.6 (*conformer **C***), 116.6 (*conformers **B**+**C***), 116.9 (*conformer **A**)*, 118.8 (*conformers **A**)*, 119.1 (*conformers **B**+**C***), 120.5 (*conformer **A**)*, 121.4 (*conformers **B**+**C***), 129.7, 151.3. MALDI TOF/TOF, m/z: 390 $[M\text{-}H]^{+}$. Anal.calcd. For $C_{21}H_{26}ClNO_4$: C, 64.36; H, 6.69; N, 3.57%. Found: C, 64.33; H, 6.67; N, 3.55%.

Cyclocondensation reactions of gem-dihydroperoxides with glyoxal catalyzed by $Sm(NO_3)_3{\cdot}6H_2O$.

General procedure: A Schlenk vessel mounted on a magnetic stirrer was charged at ~20°C with tetrahydrofuran (5 ml), glyoxal (10 mmol), and specified gem-dihydroperoxides (10 mmol).[6] Then $Sm(NO_3)_2{\cdot}6H_2O$ (0.062 g, 5 mol. % relative to 1,1'-peroxybis(1-hydroperoxycycloalkane)) was added. The reaction mixture was stirred at ~20°C for 1 h. After completion of the reaction H_2O (5 ml) and CH_2Cl_2 (5 ml) were added. The organic layer was separated, dried (anhydrous $MgSO_4$) and concentrated to isolate products stable during storage at room temperature. Products of the reaction were purified by column chromatography on SiO_2 using 10 : 1 PE : Et_2O as the eluent. The progress of reactions was monitored by TLC, with a 5 : 1 hexane : EtOAc mixture as the eluent, visualization was performed with I_2 vapor.

6,7,10,11-tetraoxaspiro[4.6]undecane-8,9-diol 18

White Solid; 0.16g (82% yield), R_f 0.79 (PE/Et_2O = 10/1), mp = 96-98°C. ^1H NMR (500.17 MHz, $CDCl_3$, 25 °C): δ = 1.72-1.80 (m, 4H, CH_2) 1.90-2.04 (m, 4H, CH_2), 5.15-5.22 (m, 2H, 2CH). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 °C): δ = 24.2, 24.3, 33.5, 33.7, 90.9, 91.1, 110.4. MALDI TOF/TOF, m/z: 191 $[M\text{-}H]^{+}$. Anal.calcd. For $C_7H_{12}O_6$: C, 43.75; H, 6.29%. Found: C, 43.73; H, 6.27%.

7,8,11,12-tetraoxaspiro[5.6]dodecane-9,10-diol 19

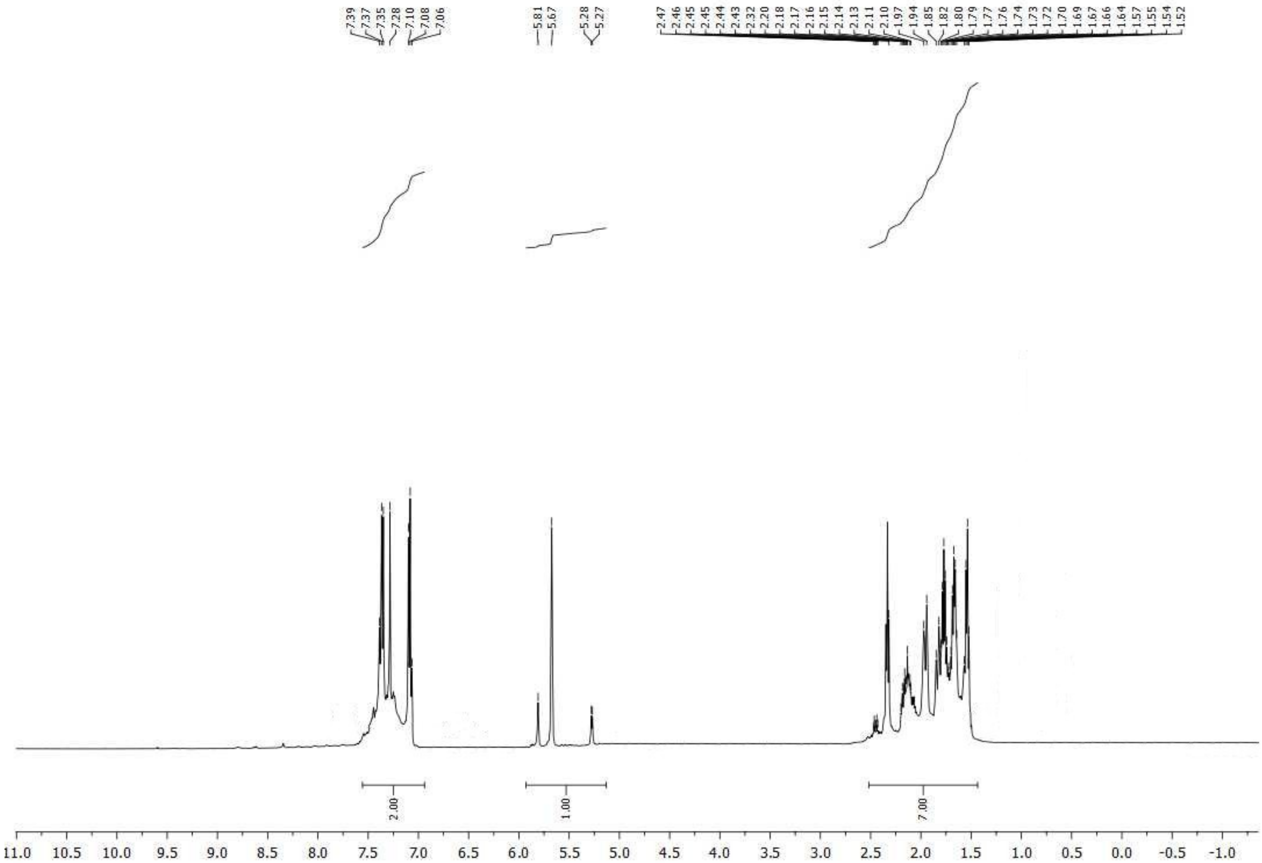
White Solid; 0.17g (85% yield), R_f 0.76 (PE/Et_2O = 10/1), mp = 54-56°C. ^1H NMR (500.17 MHz, $CDCl_3$, 25 °C): δ = 1.46-1.47 (m, 4H, CH_2), 1.59-1.64 (m, 2H, CH_2), 1.88-1.90 (m, 4H, CH_2) 5.27-5.33 (m, 2H, 2CH). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 °C): δ = 22.5, 22.6, 25.2, 25.4, 29.8, 30.7, 90.5, 91.0, 113.5. MALDI TOF/TOF, m/z: 205 $[M\text{-}H]^{+}$. Anal.calcd. For $C_8H_{14}O_6$: C, 46.60; H, 6.84%. Found: C, 46.58; H, 6.81%.

3-methyl-7,8,11,12-tetraoxaspiro[5.6]dodecane-9,10-diol 20

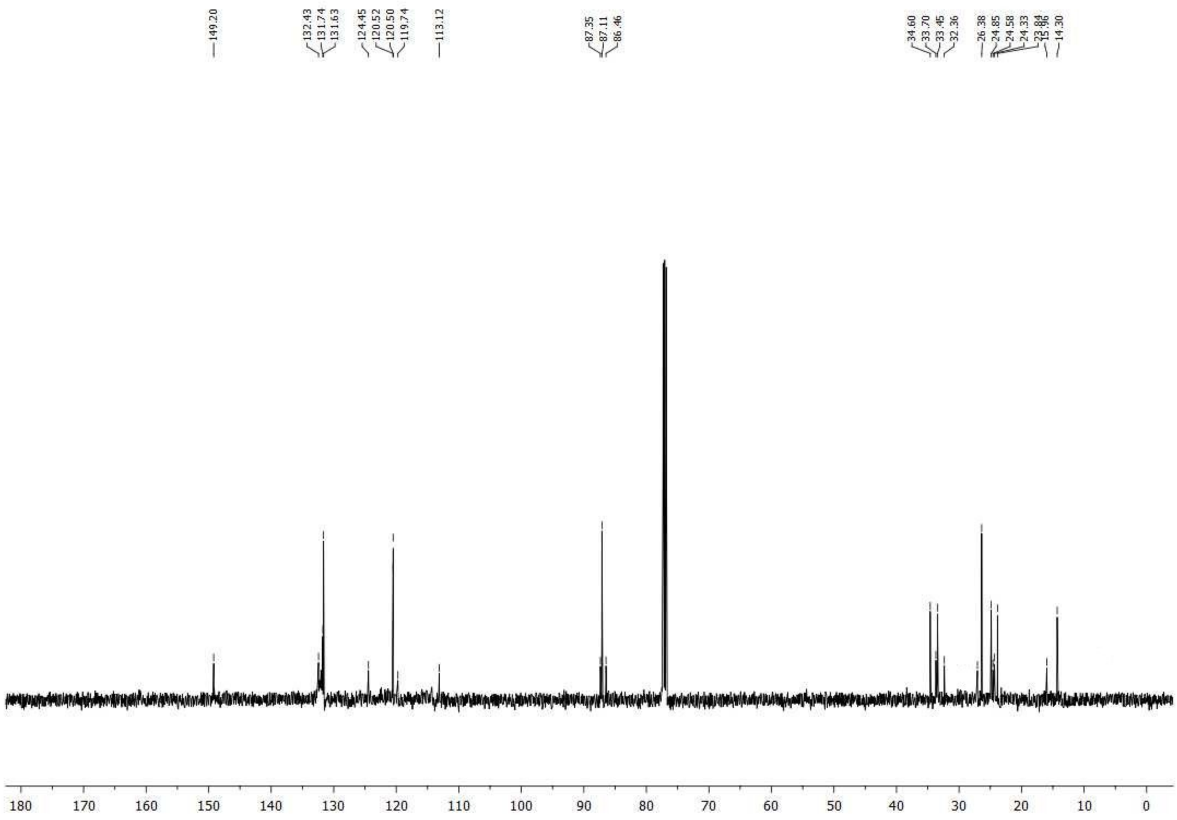
White Solid; 0.18g (85% yield), R_f 0.76 (PE/Et_2O = 10/1), mp = 68-70^oC. ^1H NMR (500.17 MHz, $CDCl_3$, 25 ^oC): δ = 0.91-0.93 (m, 3H, CH_3), 1.30-1.46 (m, 4H, CH_2), 1.61-1.62 (m, 4H, CH_2), 1.98-2.03 (m, 1H, CH) 5.20-5.35 (m, 2H, 2CH). ^{13}C NMR (125.78 MHz, $CDCl_3$, 25 ^oC): δ = 20.5, 22.6, 22.7, 25.0, 25.2, 31.2, 31.6, 32.0, 32.7, 90.3, 91.2, 113.5. MALDI TOF/TOF, m/z: 219 $[M-H]^+$. Anal.calcd. For $C_9H_{16}O_6$: C, 49.09; H, 7.32%. Found: C, 49.07; H, 7.30%.

B. Copy of NMR spectra

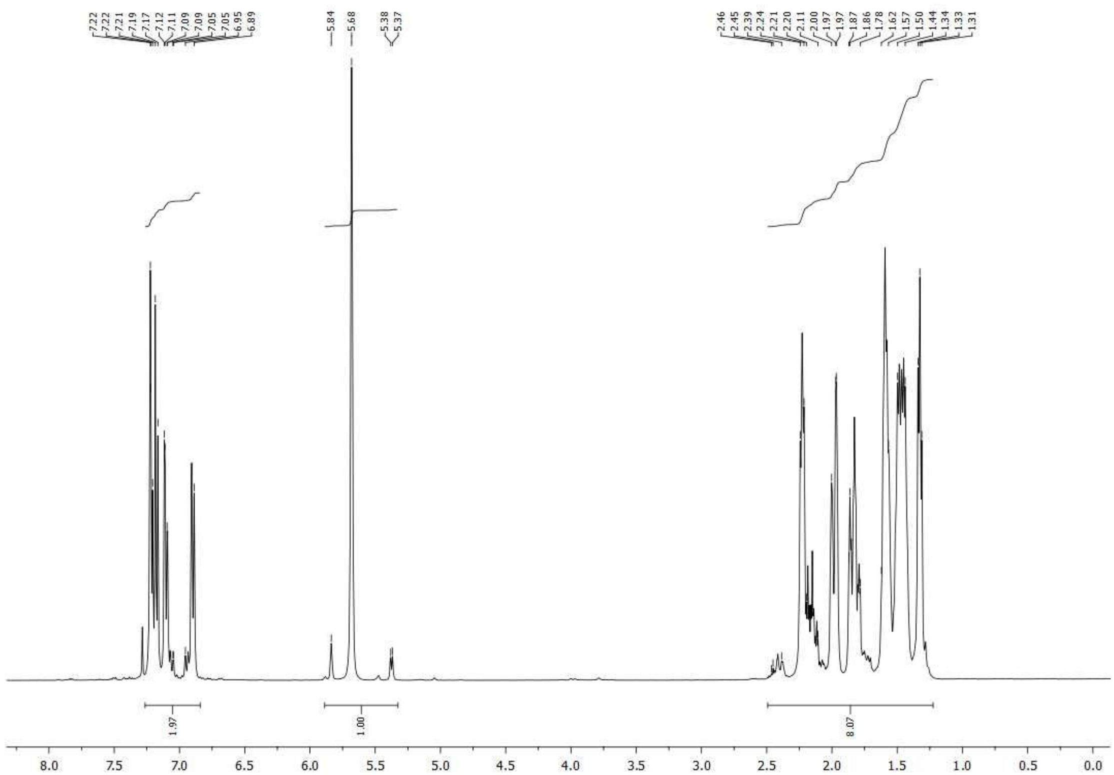
^1H-NMR spectrum of **11-(4-bromophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclopentane] 11e**



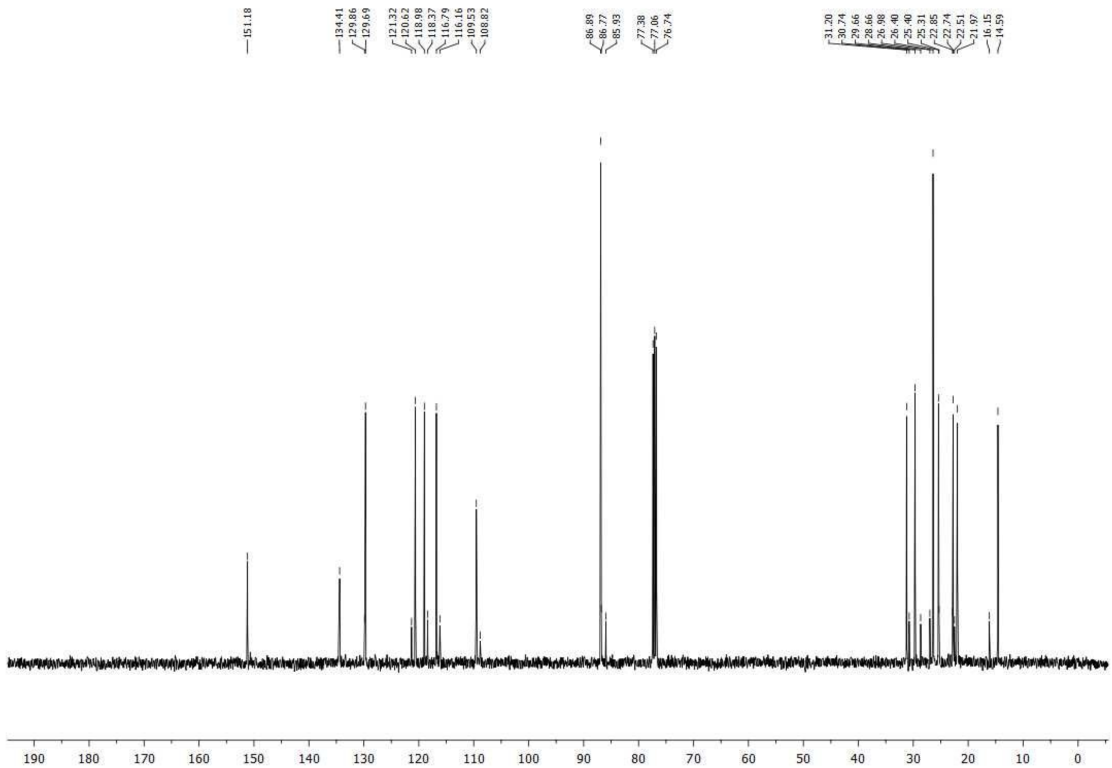
^{13}C-NMR spectrum of **11-(4-bromophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclopentane] 11e**



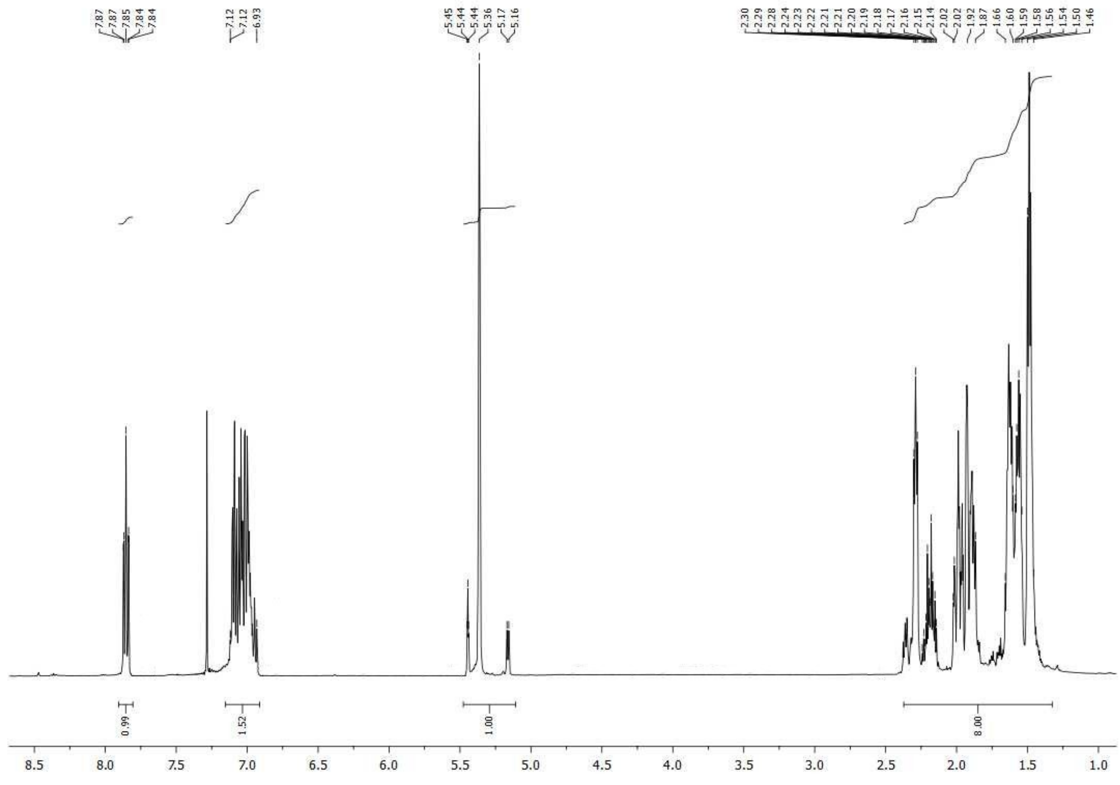
^{1}H-NMR spectrum of **11-(4-chlorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 12a**



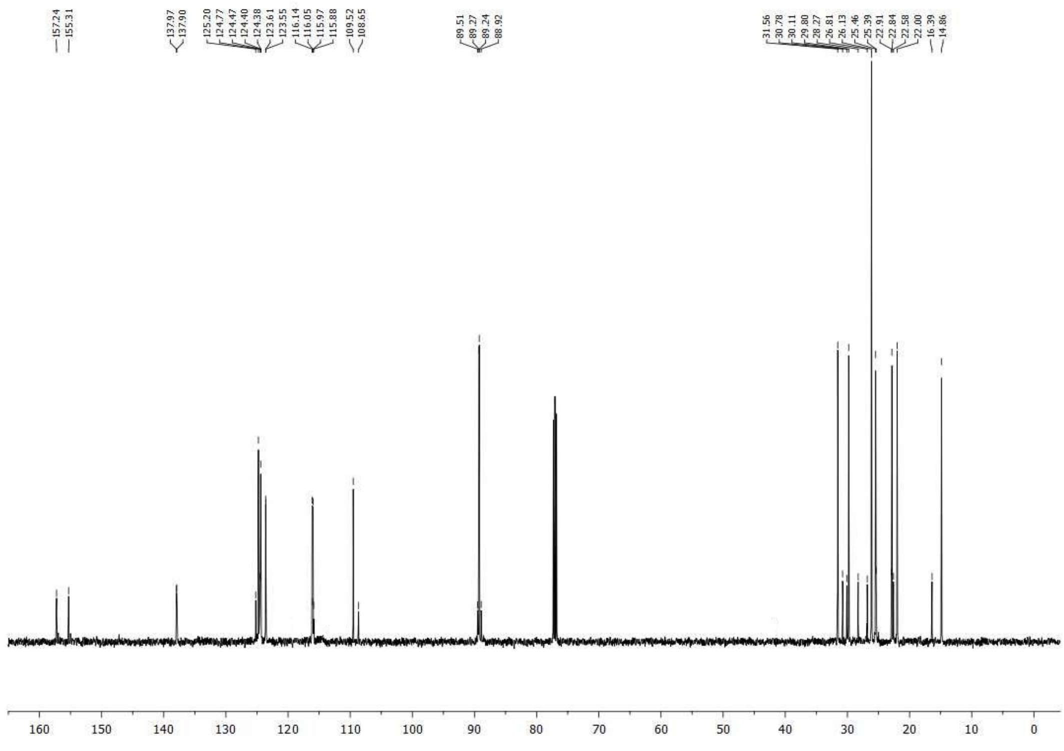
^{13}C-NMR spectrum of **11-(4-chlorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 12a**



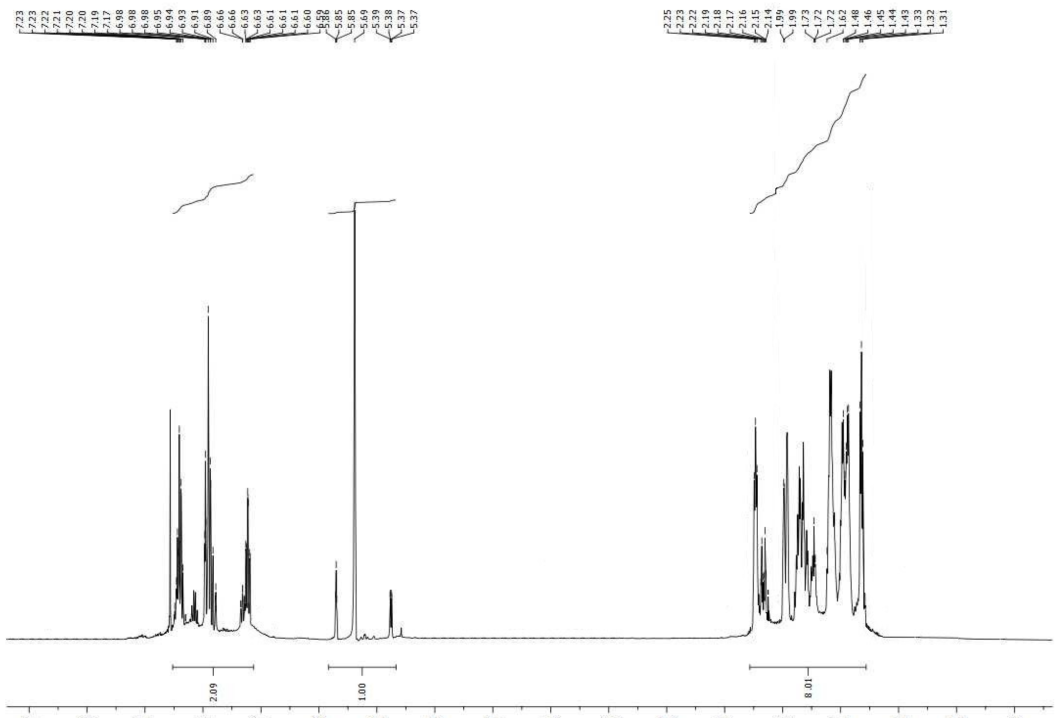
^{1}H-NMR spectrum of **11-(2-fluorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 12b**



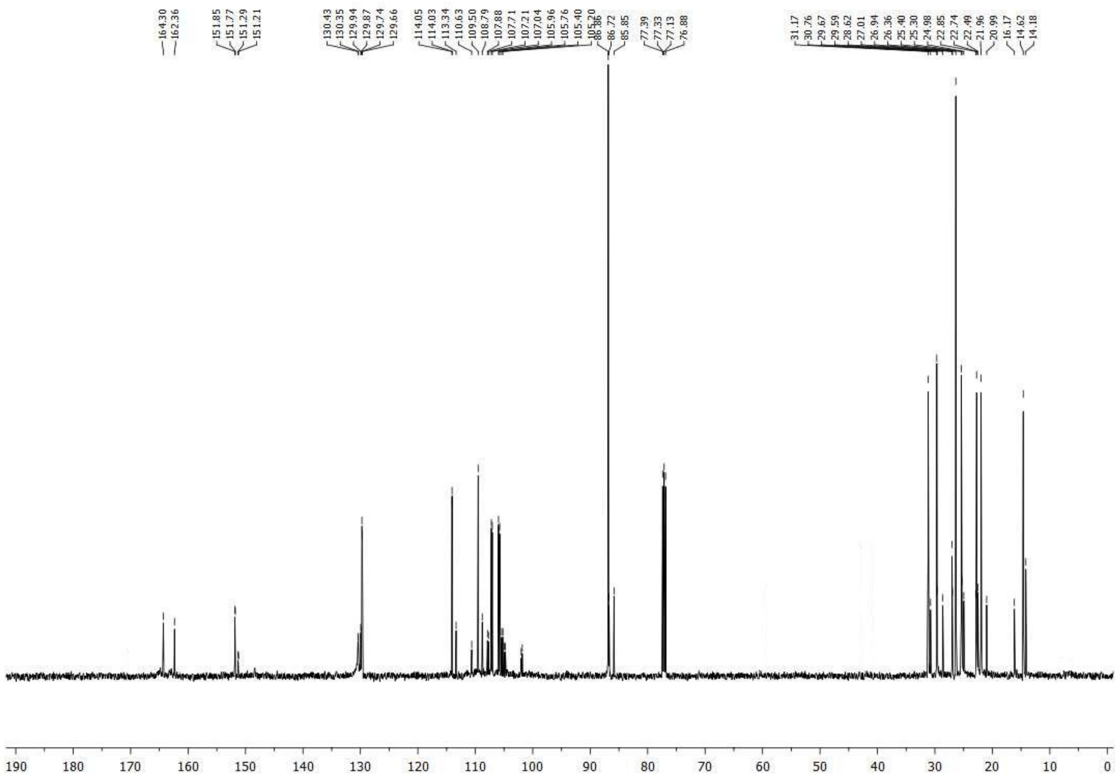
^{13}C-NMR spectrum of **11-(2-fluorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 12b**



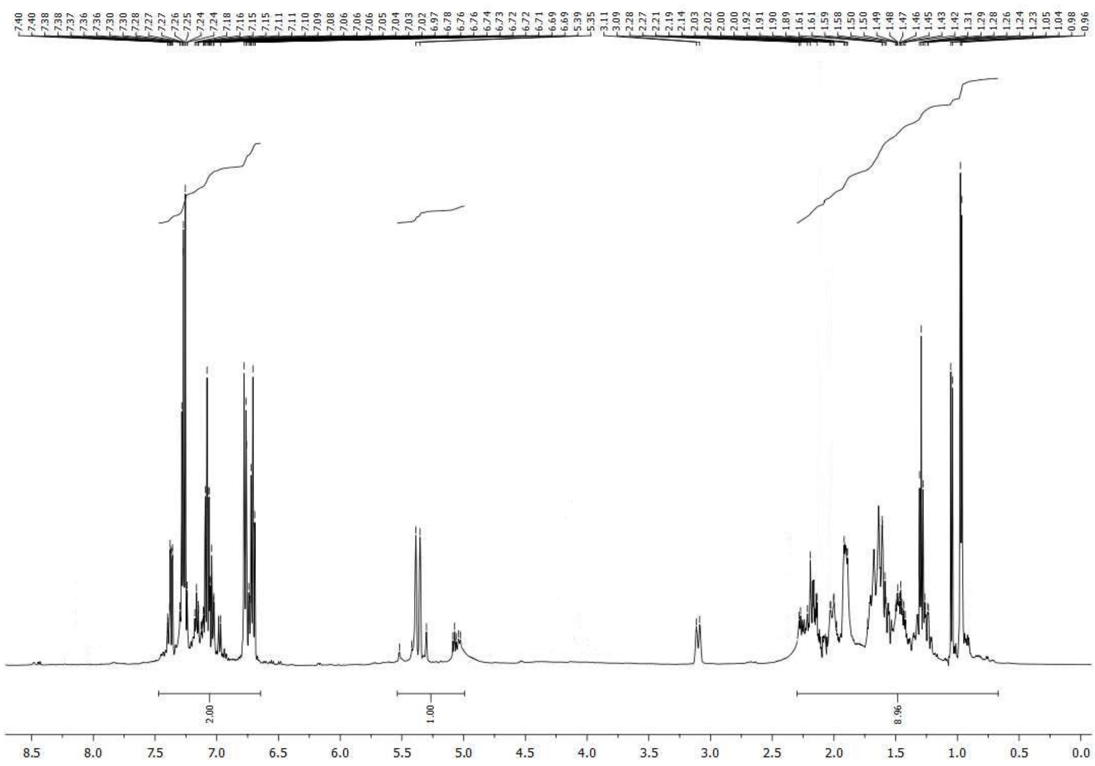
^{1}H-NMR spectrum of **11-(3-fluorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 12c**



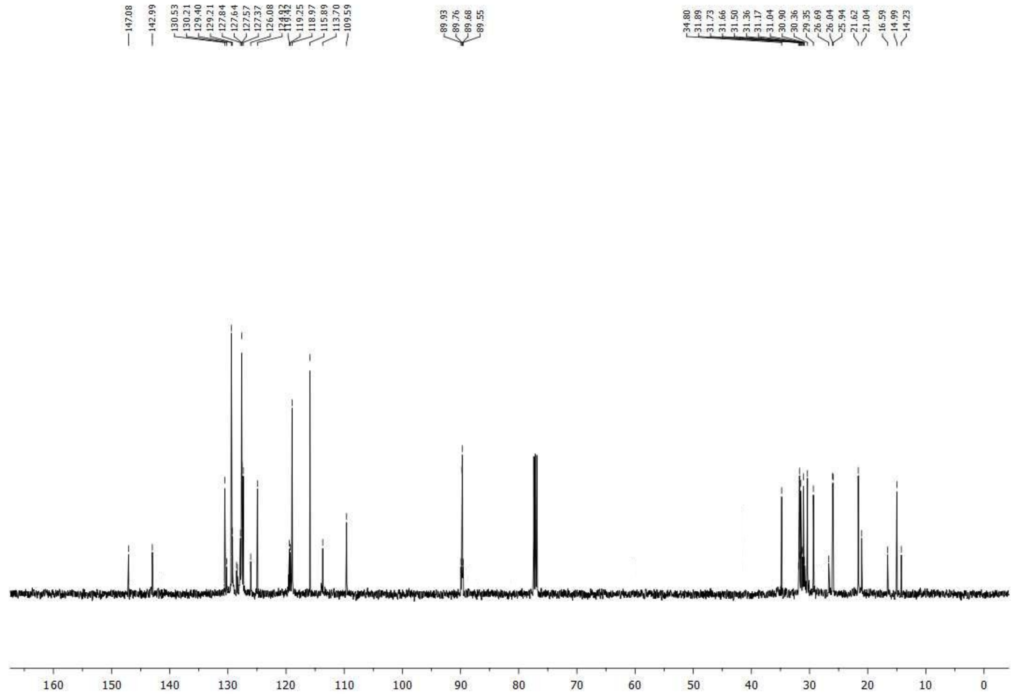
^{13}C-NMR spectrum of **11-(3-fluorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 12c**



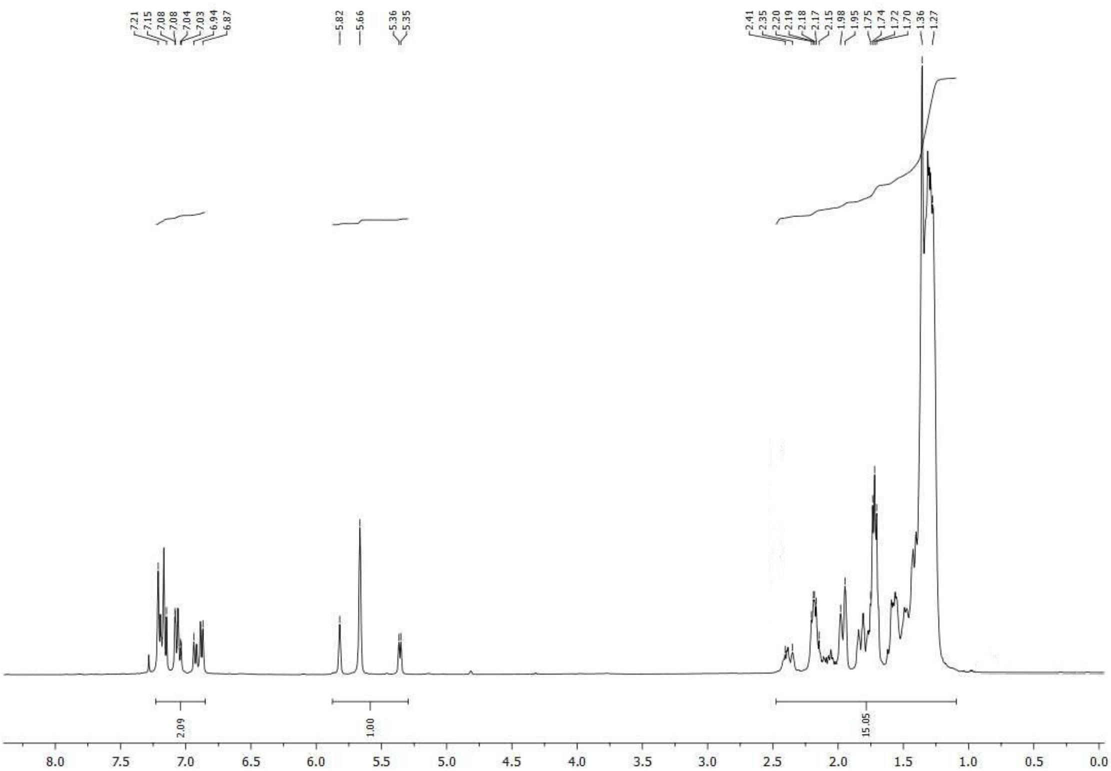
^{1}H-NMR spectrum of **11-(2-chlorophenyl)-4'-methyl-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 13f**



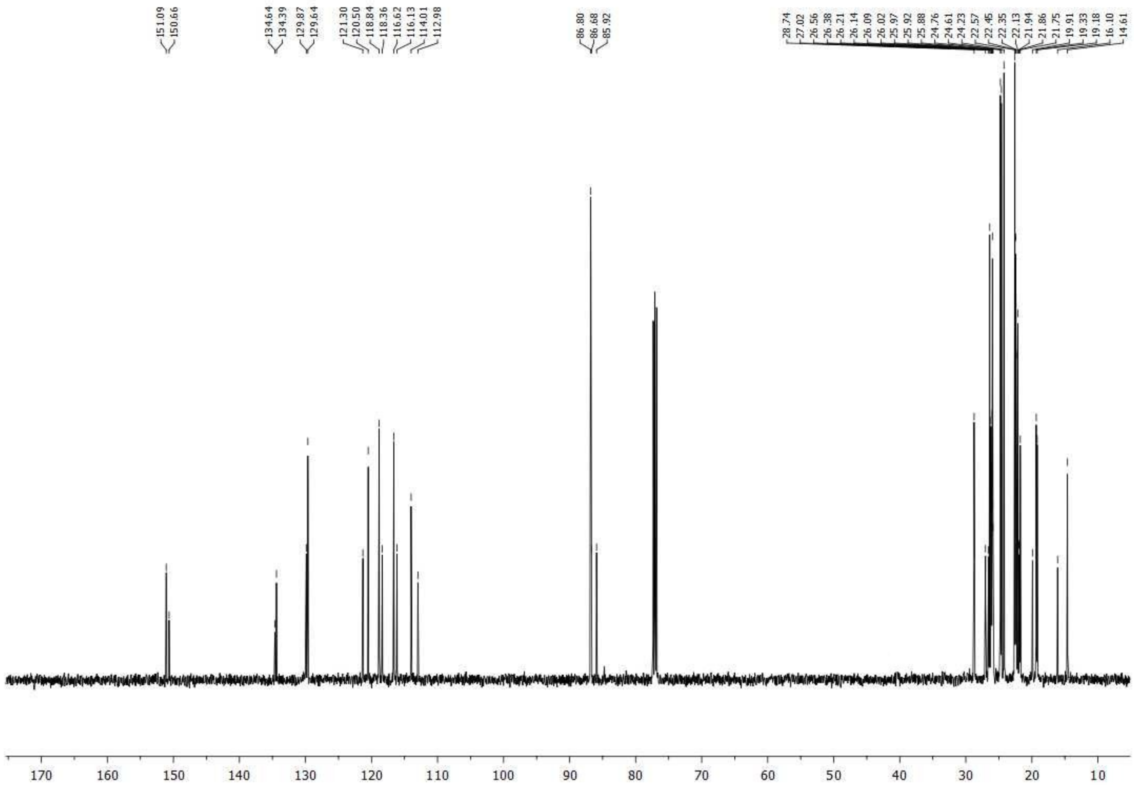
[13]C-NMR spectrum of **11-(2-chlorophenyl)-4'-methyl-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclohexane] 13f**



[1]H-NMR spectrum of **11-(2-chlorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclododecane] 15a**



^{13}C-NMR spectrum of **11-(2-chlorophenyl)-2,3,5,6-tetraoxa-11-azaspiro[bicyclo[5.3.1]undecane-4,1'-cyclododecane] 15a**



C. Crystal data and structure refinement

The crystallographic data, coordinates of atoms, and geometric parameters for compounds **4a, 4b, 4d, 4e, 12b** were deposited at the Cambridge Crystallographic Data Centre as a CIF deposition with file number CCDC 1905323, 1905327, 1905330, 1905341, 1905334, 1905337, respectively. The copies of these data are available free on demand from CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK (fax: +441223336033, e-mail: deposit@ccdc.cam.ac.uk) or through http://www.ccdc.cam.ac.uk/data_request/cif.

Crystal data for **4b**: crystals of $C_{20}H_{22}F_2N_2O_4$ (M = 392.40) are monoclinic, space group $P2_1/c$, a = 18.9061(6), b = 11.4711(4) and c = 8.7831(3) Å, β= 99.134(3)°, V = 1880.66(11) Å^3, d_{calc} = 1.386 g·cm^{-3}, Z = 4, μ = 0.110 mm^{-1}, $2\theta_{max}$ = 58.302°, 9078 reflections were measured, from which 4395 were independent. The refinement converged to R_1 = 0.0544, wR_2 = 0.1617, GOF = 1.030.

Crystal data for **4a**: crystals of $C_{20}H_{22}Cl_2N_2O_4$ (M = 425.30) are monoclinic, space group $P2_1/n$, a = 10.5362(9), b = 9.4705(6) and c = 20.3165(17) Å, β= 99.462(8)°, V = 1999.7(3) Å^3, d_{calc} = 1.413 g·cm^{-3}, Z = 4, μ = 0.354 mm^{-1}, $2\theta_{max}$ = 58.562°, 13245 reflections were measured, from which 4644 were independent. The refinement converged to $R_1 = 0.0608$, $wR_2 = 0.1313$, GOF = 0.987.

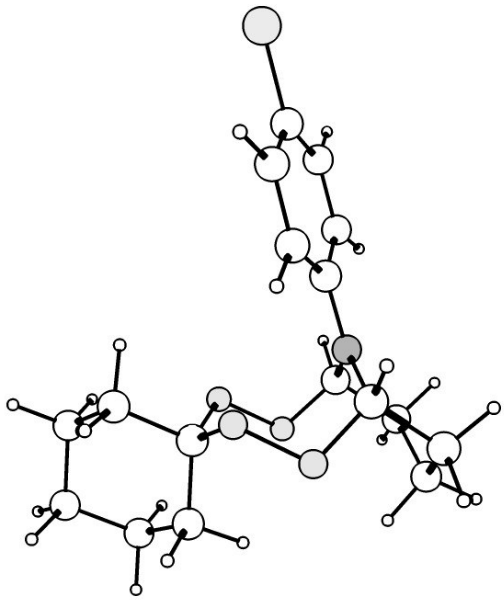
Crystal data for **4d**: crystals of $C_{20}H_{22}F_2N_2O_4$ (M = 392.40) are monoclinic, space group $P2_1/n$, a = 12.9687(13), b = 10.0294(8) and c = 14.5182(15) Å, β= 100.068(10)°, V = 1859.3(3) Å^3, d_{calc} = 1.402 g·cm^{-3}, Z = 4, μ = 0.111 mm^{-1}, $2\theta_{max}$ = 58.232°, 9607 reflections were measured, from which 4313 were independent. The refinement converged to $R_1 = 0.0825$, $wR_2 = 0.2015$, GOF = 1.026.

Crystal data for **4e**: crystals of $C_{20}H_{22}Br_2N_2O_4$ (M = 514.20) are monoclinic, space group $P2_1/n$, a = 10.6640(6), b = 9.4362(6) and c = 20.7558(11) Å, β= 97.997(5)°, V = 2068.3(2) Å^3, d_{calc} = 1.651 g·cm^{-3}, Z = 4, μ = 3.948 mm^{-1}, $2\theta_{max}$ = 58.354°, 9852 reflections were measured, from which 4798 were independent. The refinement converged to $R_1 = 0.0749$, $wR_2 = 0.1295$, GOF = 0.986.

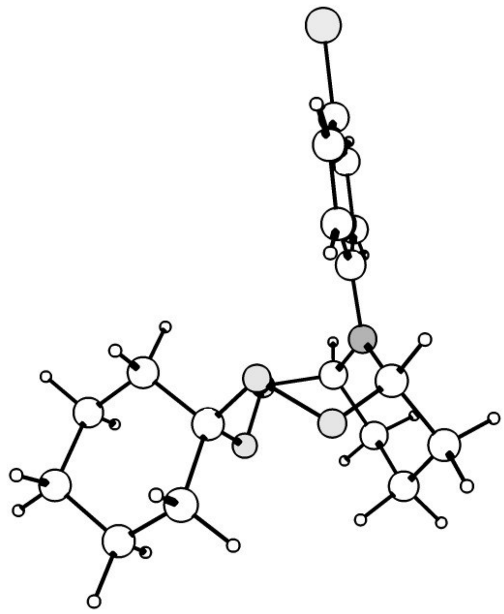
Crystal data for **12b**: crystals of $C_{17}H_{22}FNO_4$ (M = 323.36) are triclinic, space group P-1, a = 6.4738(3), b = 10.2056(9) and c = 12.4931(10) Å, α = 75.029(7)°, β= 80.670(6)°, γ = 88.090(6)°, V = 786.81(11) Å^3, d_{calc} = 1.365 g·cm^{-3}, Z = 2, μ = 0.104 mm^{-1}, $2\theta_{max}$ = 58.558°, 6506 reflections were measured, from which 3611 were independent. The refinement converged to $R_1 = 0.0503$, $wR_2 = 0.1115$, GOF = 1.061.

Crystal data for **19**: crystals of $C_8H_{14}O_6$ (M = 206.19) are orthorhombic, space group Pbca, a = 6.5986(6), b = 9.8591(8) and c = 29.604(2) Å, α =90°, β= 90°, γ = 90°, V = 1925.9(3) Å^3, d_{calc} = 1.422 g·cm^{-3}, Z = 8, μ = 0.123 mm^{-1}, $2\theta_{max}$ = 58.102°, 4693 reflections were measured, from which 1905 were independent. The refinement converged to $R_1 = 0.0953$, $wR_2 = 0.2238$, GOF = 0.980.

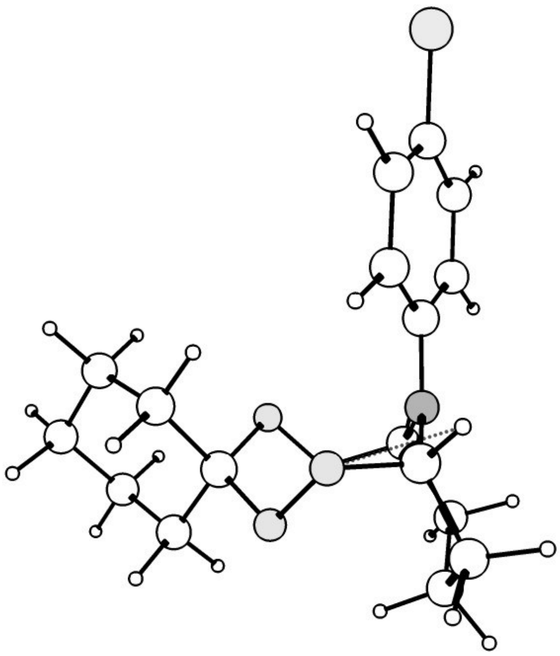
Figure 1 Optimized structures of the lowest energy conformers of tetraoxazaspirobicycloalkanes.



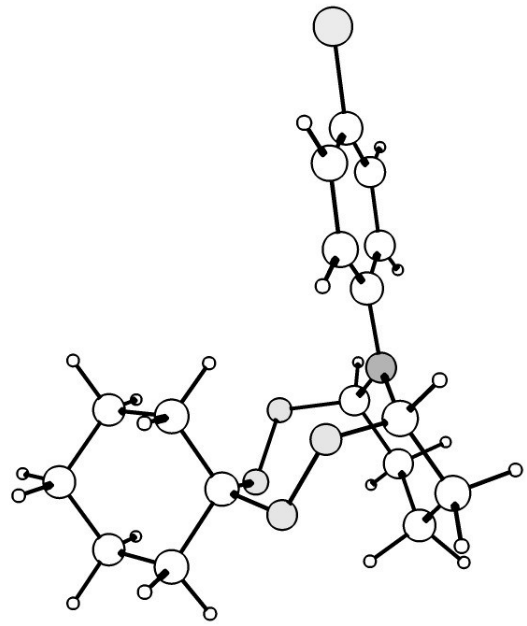
A 0.0 Kcal/mol



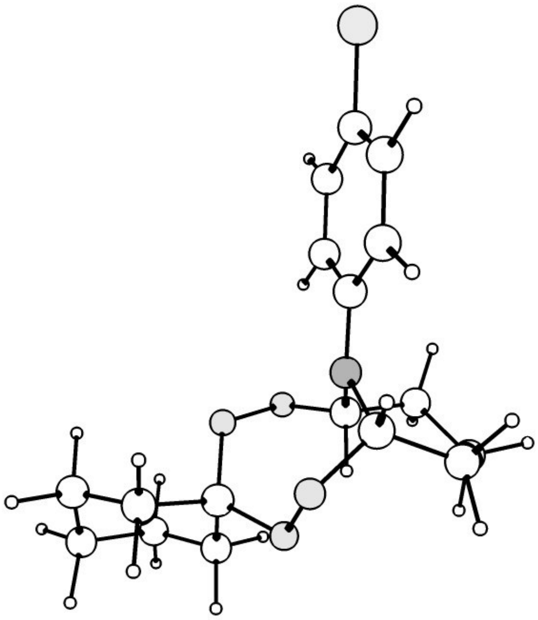
B 0.9 Kcal/mol



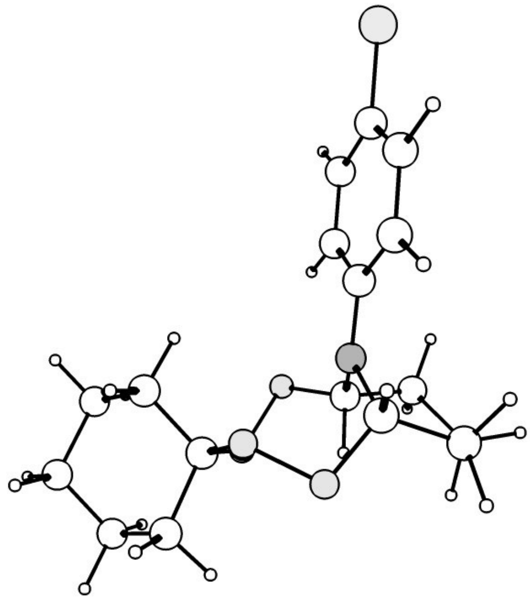
B′ 1.0 Kcal/mol



C 3.5 Kcal/mol



D 28.7 Kcal/mol



E 31.4 Kcal/mol

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