Electronic Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supporting Information for:

Mild Preparation of Functionalized [2.2]Paracyclophanes via the Pummerer Rearrangement

*Matteo Montanari, Alberto Bugana, Arvind K. Sharma and Dario Pasini**

Department of Chemistry and INSTM Research Unit, University of Pavia, Viale Taramelli, 10 – 27100 Pavia –Italy. Email: dario.pasini@unipv.it

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1. Experimental section

1.1 General. Anthranilic acid was recrystallized before use. All other commercially available reagents and solvents were used as received, including technical grade *m*-CPBA. THF (Na, benzophenone) and CH_2Cl_2 (CaH_2) were dried and distilled before use. 1,2-Dichloroethane, chloroform and benzene were dried using 4Å molecular sieves. Lithium diisopropylamide (LDA) was obtained in situ by addition of a solution of *n*-BuLi (ca. 0.8 eq) to a solution of isopropylamine (previously distilled over CaH_2) in dry THF under nitrogen at -78°C, then stirred at room temperature for 20 min and transferred via a cannula to the reaction flask. Compounds **2**,[S1] **7** and **8**,[S2] were obtained following previously published procedures. Compound **6** was synthesized following either of published routes,[S3,S4] of which the former is much more convenient and faster on a relatively small scale (1-2 g). Flash chromatography was carried out using silica gel (Merck 60). ^1H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ or CD_3COCD_3 on Bruker 200 or AMX300 with the solvent residual proton signal or tetramethylsilane (TMS) as a standard. Gas chromatography-mass spectrometry (GC-MS) was performed using a HP-5 type column; carrier gas: nitrogen; temperature range: 100-250°C; 10°C min^{-1} increasing rate. In the case of **20**, the mixture did not fly on GC, and the mass spectrum was obtained by direct injection. The photochemical experiments were performed in a multilamp apparatus fitted with 6 low-pressure mercury lamps.

General Preparation of Benzylic Dithiols. Compound 3. A solution of benzylic dibromide **6** (0.2 g, 0.6 mmol, 1 eq) in EtOH (15 mL) was combined with thiourea (0.19 g, 2.5 mmol, 4 eq) and the suspension was stirred at reflux for 12 h. The solvents were removed *in vacuo*, a solution of NaOH (0.4 g, 10 mmol, 4 eq) in H_2O (10 mL) was added and the suspension was refluxed for 4 h. After cooling to 0°C, a solution of HCl 6N was slowly added until pH=2. The aqueous layer was then

extracted with $CHCl_3$ (3 x 50 mL), and the organic layer dried (Na_2SO_4). The product **3** (0.1 g, 69%) obtained after the workup described above did not require purification column chromatography. ^{1}H-NMR ($CDCl_3$, 200 MHz, 25°C) δ = 3.80 (d, 4H; benzylic CH_2), 2.09 (t, 2H; -SH). This compound has been previously reported.[S5] **Compound 4**. From benzylic dibromide **7** (2.0 g, 6.17 mmol, 1 eq) in EtOH (50 mL) and THF (150 mL) and thiourea (1.22 g, 16.04 mmol, 2.5 eq). The product was purified by column chromatography (SiO_2; hexanes, then hexanes:Et_2O/8:2) to afford **4** as a white solid (194 mg, 28%). R_f: 0.4 (hexanes:Et_2O/8:2). ^{1}H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 6.81 (s, 2H; aryl), 3.86 (s, 6H; ArOCH_3), 3.70 (d, 4H; benzylic CH_2). This compound has been previously reported.[S6]

General procedure for the preparation of [3.3]dithiaparacyclophanes. Compound 9. A solution of the benzylic dithiol **2** (1 g, 5.87 mmol, 1 eq, 0.05 M) and the benzylic dibromide **5** (1.55 g, 5.87 mmol, 1 eq, 0.05 M) in benzene (118 mL) was added dropwise using a pressure equalizing funnel under vigorous magnetic stirring during a period of 72 h to a solution of KOH (0.73 g, 12.9 mmol, 2.2 eq, 0.05 M) in EtOH (258 mL). The solvents were then removed *in vacuo*, $CHCl_3$ (150 mL) was added, and the organic layer washed with a saturated $NaHCO_3$ solution, a HCl 1 M aqueous solution, and brine. The organic layer was then dried (Na_2SO_4), and the product purified by column chromatography (SiO_2; hexanes:CH_2Cl_2/9:1 to 8:2) to afford **9** as a white solid (700 mg, 51%). R_f: 0.35 (hexanes:CH_2Cl_2/8:2). ^{1}H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 6.88 (s, 8H; aryl), 3.83 (s, 8H; benzylic CH_2). This compound has been previously reported.[S7] **Compound 10.** From benzylic dithiol **3** (99 mg, 0.407 mmol, 1 eq, 0.02 M) and benzylic dibromide **6** (136 mg, 0.407 mmol, 1 eq, 0.02 M). The product was purified by column chromatography (SiO_2; hexanes:CH_2Cl_2/7:3) to afford **10** as a white solid (140 mg, 82%). ^{1}H-NMR ($CDCl_3$, 200 MHz, 25°C) δ = 3.99 (s, 8H; benzylic CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ = 144.4 (dm, J = 256 Hz), 114.8 (m), 24.7. This compound has been previously reported.[S5] **Compound 11.** From

benzylic dithiol **2** (81 mg, 0.48 mmol, 1 eq, 0.05 M) and the benzylic dibromide **6** (160 mg, 0.48 mmol, 1 eq, 0.05 M) in THF (10 mL). The product was purified by column chromatography (SiO_2; hexanes:CH_2Cl_2/9:1) to afford **11** as a white solid (40 mg, 30%). R_f: 0.3 (hexanes:CH_2Cl_2/9:1). ^{1}H-NMR ($CDCl_3$, 300 MHz, 25°C) δ = 7.24 (s, 4H; aryl), 3.89 (s, 4H; benzylic CH_2), 3.81 (s, 4H; benzylic CH_2). ^{13}C-NMR ($CDCl_3$, 75 MHz, 25°C) δ = 143.7 (dm, J = 242 Hz), 135.0, 128.6, 115.1 (m), 37.3, 24.1. This compound has been previously reported.[S5] **Compound 12.** From benzylic dithiol **2** (1 g, 5.87 mmol, 1 eq, 0.05 M) and benzylic dibromide **7** (1.9 g, 5.87 mmol, 1 eq, 0.05 M) in THF. The product was purified by column chromatography (SiO_2; hexanes:CH_2Cl_2/6:4) to afford **12** as a white solid (1.7 g, 71%). R_f: 0.7 (hexanes:CH_2Cl_2/6:4). ^{1}H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 6.97 (m, 4H; aryl), 6.48 (s, 2H; aryl), 4.27 (d, 2H; benzylic CH_2), 3.90-3.70 (s, 10H; O$\underline{CH_3}$ and benzylic CH_2), 3.43-3.35 (d, 2H; benzylic CH_2). This compound has been previously reported.[S8] **Compound 13.** From benzylic dithiol **2** (1 g, 5.87 mmol, 1 eq, 0.05 M) and the benzylic dibromide **8** (2.72 g, 5.87 mmol, 1 eq, 0.05 M). The product was purified by column chromatography (SiO_2; hexanes:AcOEt/99:1) to afford **13** as a white waxy solid (1.4 g, 50%). ^{1}H-NMR ($CDCl_3$, 200 MHz, 25°C) δ = 6.94 (m, 4H; aryl), 6.44 (s, 2H; aryl), 4.29 (d, 2H; benzylic CH_2), 3.94-3.73 (m, 8H; -O$\underline{CH_2}CH_2$- and benzylic CH_2), 3.37 (d, 2H; benzylic CH_2), 1.82 (m, 4H; -$OCH_2\underline{CH_2}CH_2$-), 1.45 (m, 12H; -$C\underline{H_2}$-), 0.93 (t, 6H; -$C\underline{H_3}$). ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ = 149.7, 135.4, 128.9, 128.0, 124.8, 114.4, 68.1, 37.8, 31.6, 31.0, 29.5, 26.0, 22.6, 14.0. Anal. calcd. for $C_{28}H_{40}O_2S_2$: C 71.1%, H 8.5%; found: C 71.5%, H 8.4%. **Compound 14.** From benzylic dithiol **4** (194 mg, 0.6 mmol, 1 eq, 0.05 M) and benzylic dibromide **6** (200 mg, 0.6 mmol, 1 eq, 0.05 M) in THF. The product was purified by column chromatography (SiO_2; hexanes:Et_2O/9:1) to afford **14** as a white solid (102 mg, 42%). R_f : 0.3 (hexanes:Et_2O/9:1). ^{1}H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 6.88 (s, 2H; aryl), 4.38-3.47 (m, 14H; ArO$\underline{CH_3}$ and benzylic CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz, 25°C) δ = 151.2, 144.1 (dm), 114.6 (m), 112.2, 55.8 (-OCH_3), 30.9 (CH_2), 24.3 (CH_2). MS-ESI *m/z* (%): 405 ($[M + H]^+$, 100). Anal. calcd. for $C_{18}H_{16}F_4O_2S_2$: C 53.5%, H 4.0%; found: C 53.2%, H 4.2%.

General procedure for the Pummerer Rearrangement. Compound 15. *m*-CPBA (172 mg, 0.4 mmol, 2.2 eq) was added to a solution of the dithiacyclophane **9** (50 mg, 0.18 mmol, 1 eq) in $CHCl_3$ (25 mL) and the solution was stirred under N_2 overnight at room temperature. The organic solution was then washed with a saturated $NaHCO_3$ solution (50 mL), dried (Na_2SO_4), and the solvent removed *in vacuo* to give the disulfoxide (55 mg, 100%) as a white solid, which was analyzed by NMR spectroscopy and used without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 6.98 (m, 8H; aryl), 4.54-4.01 (m, 8H; benzylic CH_2). A solution of the disulfoxide (47 mg, 0.15 mmol) was dissolved in acetic anhydride (20 mL) in the presence of a catalytic amount of NaOAc and heated at 130°C with magnetic stirring for 5 h. The solvent was removed *in vacuo*, the residue dissolved in $CHCl_3$, washed with a saturated $NaHCO_3$ solution, the organic layer dried (Na_2SO_4), and the solvent removed *in vacuo*. The product was purified by column chromatography (SiO_2; hexanes, then hexanes:AcOEt/9:1) to afford **15** as a white solid (30 mg, 51%). R_f: 0.5-0.45 (hexanes:AcOEt/8:2). Two different spots could be isolated in this case having identical NMR spectra: ^{1}H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 7.01-6.74 (m, 10H; -SC<u>H</u>OAc and aryl), 4.15-3.75 (dd, 4H; benzylic CH_2), 2.27 (s, 6H; OCOC<u>H</u>$_3$). **Compound 16.** From *m*-CPBA (300 mg, 0.96 mmol, 2.2 eq) and dithiacyclophane **11** (150 mg, 0.43 mmol, 1 eq) in $CHCl_3$ (50 mL) to give the disulfoxide (150 mg, 93%) as a white solid, which was analyzed by NMR and used without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 7.33-7.16 (m, 4H; aryl), 4.62-3.63 (m, 8H; benzylic CH_2). From a solution of the disulfoxide (159 mg, 0.39 mmol) dissolved in acetic anhydride (70 mL). The product was purified by column chromatography (SiO_2; hexanes, then hexanes:AcOEt/8:2) to afford **16** as a white solid (100 mg, 56%). R_f: 0.6 (hexanes:AcOEt/8:2). ^{1}H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 7.22-7.18 (m, 4H; aryl), 6.91 (m, 2H; SC<u>H</u>OAc), 4.20-3.50 (m, 6H; benzylic CH_2), 2.30-2.10 (m, 6H; OCOC<u>H</u>$_3$). **Compound 17.** From *m*-CPBA (340 mg, 0.108 mmol, 2.2 eq) and dithiacyclophane **13** (233 mg, 0.49 mmol, 1 eq) in $CHCl_3$ (50 mL) to give the

disulfoxide (270 mg, 100%) which was analyzed by NMR and used without further purification. ^{1}H-NMR ($CDCl_3$, 200 MHz, 25°C) δ = 6.95 (m, 4H; aryl), 6.35 (m, 2H; aryl), 4.65-4.33 (m, 4H; benzylic CH_2), 4.13-3.68 (m, 8H; -OC$\underline{H}_2$CH_2 and benzylic CH_2), 1.82 (m, 4H; -OCH_2C$\underline{H}_2$CH_2-), 1.4-1.2 (m, 12H; -C$\underline{H}_2$-), 0.93 (m, 6H; -C$\underline{H}_3$). From a solution of the disulfoxide (270 mg, 0.55 mmol) dissolved in acetic anhydride (100 mL). The product was purified by column chromatography (SiO_2; hexanes:AcOEt/9:1) to afford **17** as a white waxy solid (156 mg, 48%). R_f: 0.5-0.45 (hexanes:AcOEt/8:2). ^{1}H-NMR ($CDCl_3$, 200 MHz, 25°C) δ = 7.10-6.24 (m, 8H; aryl and SC$\underline{H}$OAc), 4.18-3.23 (m, 8H; -OC$\underline{H}_2$CH_2- and benzylic CH_2), 2.23 (m, 6H; -O$\underline{Ac}$), 1.85 (m, 4H; -OCH_2C$\underline{H}_2$CH_2-), 1.45 (m, 12H; -C$\underline{H}_2$-), 0.97 (m, 6H; -C$\underline{H}_3$).

General procedure for the Photochemical Sulfur Extrusion. Compound 18. A solution of compound **15** (23 mg, 0.06 mmol) in benzene (3.2 mL) and $P(OEt)_3$ (1.8 mL) in a 10 mL quartz cuvette was deareated by bubbling N_2 for 10 min. The cuvette was then irradiated for 8 h. After removing the solvents *in vacuo*, the mixture was purified by column chromatography (SiO_2; hexanes:AcOEt/9:1) to afford **18** as a white solid (12 mg, 100%). R_f: 0.5 (hexanes:AcOEt/8:2). ^{1}H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 6.91-6.46 (m, 8H; aryl), 6.18 (s, 2H; ArC$\underline{H}$OAc), 3.69 (m, 2H; benzylic CH_2), 2.92 (m, 2H; benzylic CH_2), 2.24 (s, 6H; OCOC$\underline{H}_3$). GC-MS *m/z* (%): 265 ([*M* – AcOH]$^+$, 15), 223 ([*M* – $CH_2C_6H_4CH_2$]$^+$, 100). **Compound 19.** From compound **16** (36 mg, 0.06 mmol) in benzene (6.4 mL) and $P(OEt)_3$ (3 mL). The mixture was purified by column chromatography (SiO_2; hexanes:Et_2O/9:1) to afford **19** as a white solid (30 mg, 70%). R_f: 0.35 (hexanes:Et_2O/9:1). ^{1}H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 7.38-6.80 (m, 4H; aryl), 6.19 (m, 2H; ArC$\underline{H}$OAc), 3.87-3.78 (m, 2H; benzylic CH_2), 3.54-2.90 (m, 2H; benzylic CH_2), 2.18 (m, 6H; OCOC$\underline{H}_3$). GC-MS *m/z* (%): 337 ([*M* – AcOH]$^+$, 30), 295 ([*M* – AcOH – Ac]$^+$, 100). **Compound 20.** From compound **17** (46 mg, 0.1 mmol) in benzene (3.2 mL) and $P(OEt)_3$ (1.8 mL). The mixture was purified by column chromatography (SiO_2; hexanes:Et_2O/9:1) to afford **20** as a white waxy

solid (30 mg, 70%).R_f : 0.35 (hexanes:Et_2O/9:1). ^1H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 7.13-5.57 (m, 8H; aryl and ArC<u>H</u>OAc), 4.01-3.72 (m, 4H; benzylic CH_2 and -OC<u>H_2</u>CH_2), 2.23 (m, 6H; OCOC<u>H_3</u>), 1.90-0.9 (m, 22H, -C<u>H_2</u>- and -C<u>H_3</u>). GC-MS *m/z* (%): 526 ($[M + 2H]^+$, 70) 465 ($[M – OAc]^+$, 70), 423 ($[M – OAc – Ac]^+$, 100).

Cyclophanediene 1. Conventional route.[S7] A solution of freshly recrystallized anthranilic acid (251 mg, 1.83 mmol, 2.5 eq, 50 mM) in dry 1,2-dichloroethane (36.5 mL) was added dropwise under N_2 at reflux (70°C) during 3 h to a solution of thiacyclophane **9** (200 mg, 0.73 mmol, 1 eq, 20 mM) and isoamyl nitrite (0.9 mL, 6.53 mmol, 8.95 eq) in dry 1,2-dichloroethane (36.5 mL). After cooling to room temperature, the solvent was removed *in vacuo*, and the residue was purified by column chromatography (SiO_2; hexanes:AcOEt/9:1) to afford the Stevens rearranged products (mixture of regio and stereoisomers) **9a** (176 mg, 56%) as a viscous oil. R_f: 0.3 (hexanes:AcOEt/9:1). ^1H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 7.46-6.53 (m, 18H; aryl), 4.78-4.62 (m, 2H; ArC<u>H</u>SPh), 4.01-3.54 (m, 4H, benzylic CH_2). *m*-CPBA (184 mg, 0.91 mmol, 2.2 eq) was added to a solution of the Stevens rearranged product **9a** (176 mg, 0.41 mmol, 1 eq) in $CHCl_3$ (40 mL) and the solution was stirred under N_2 overnight at room temperature. The organic solution was then washed with a saturated $NaHCO_3$ solution (50 mL), dried (Na_2SO_4), and the solvent removed *in vacuo* to give the disulfoxide **9b** (189 mg, 100%) which was analyzed by NMR and used without further purification. A solution of disulfoxide **9b** (189 mg, 0.41 mmol) in xylene (80 mL) was refluxed (140°C) for 24 h. The solvent is removed *in vacuo*, and the reaction mixture is purified by column chromatography (SiO_2; hexanes:benzene/5:5) to afford **1** as a white solid (18 mg, 22%). ^1H NMR ($CDCl_3$, 200 MHz, 25°C) δ = 7.22 (s, 4H; vinyl), 6.52 (s, 8H; aryl). **Alternative procedure for 1 from compound 9a.** A solution of **9a** (69 mg, 0.16 mmol, 1 eq) in CH_2Cl_2 (10 mL) is cooled to 0°C. $Me_3O^+ \bullet BF_4^-$ (53 mg, 0.36 mmol, 2.2 eq) is added as a solid, and the mixture is left stirring at 0°C for 2h, then at room temperature for 12 h. KO*t*Bu (76 mg, 0.68 mmol, 4.2 eq) in THF (3 mL) is

then added and the mixture is stirred for a further 12 h. The reaction is quenched with NH_4Cl (17 mL), the organic layer is separated and the aqueous layer is washed with CH_2Cl_2 (3x20 mL). The combined organic layers are dried (Na_2SO_4) and the product purified by column chromatography to give the desired product **1** (7 mg, 21%).

Cyclophanediene 1. New route from compound 18. Freshly prepared LDA (85 eq) in THF was transferred via a cannula under nitrogen to a solution of **18** (27 mg, 0.08 mmol) in dry benzene (7 mL). The solution was left stirring at room temperature for 24 h. The solvent were removed *in vacuo*, and the solid taken in Et_2O (100 mL), and washed with a saturated NH_4Cl aqueous solution. The organic layer was dried, and the product purified by column chromatography (SiO_2; hexanes, then hexanes:Et_2O/9:1) to give **1** (10 mg, 58%).

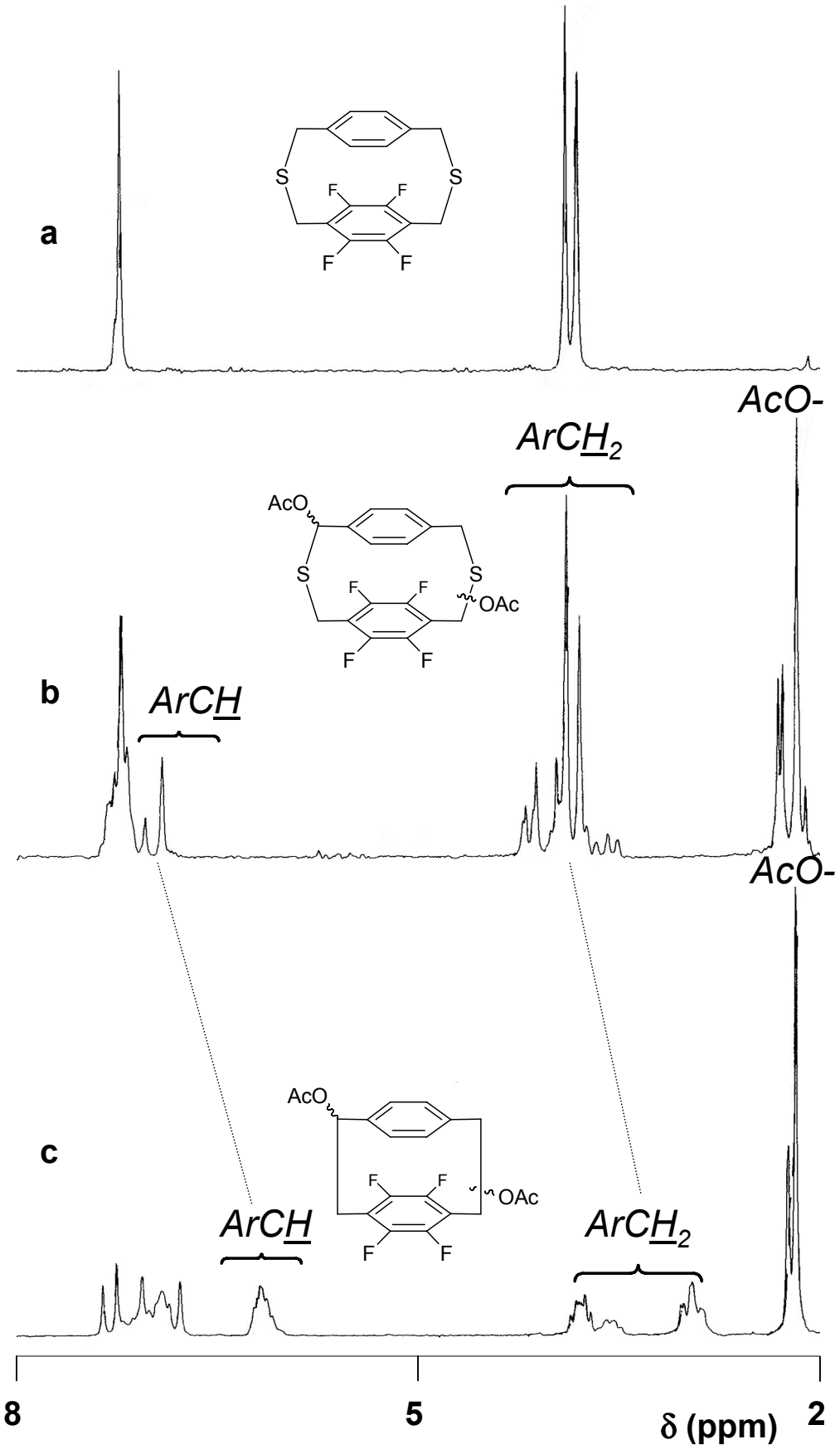


Figure S1. ^{1}H NMR (200 MHz, $CDCl_3$) of compounds: a) **11**; b) **16**; c) **19**.

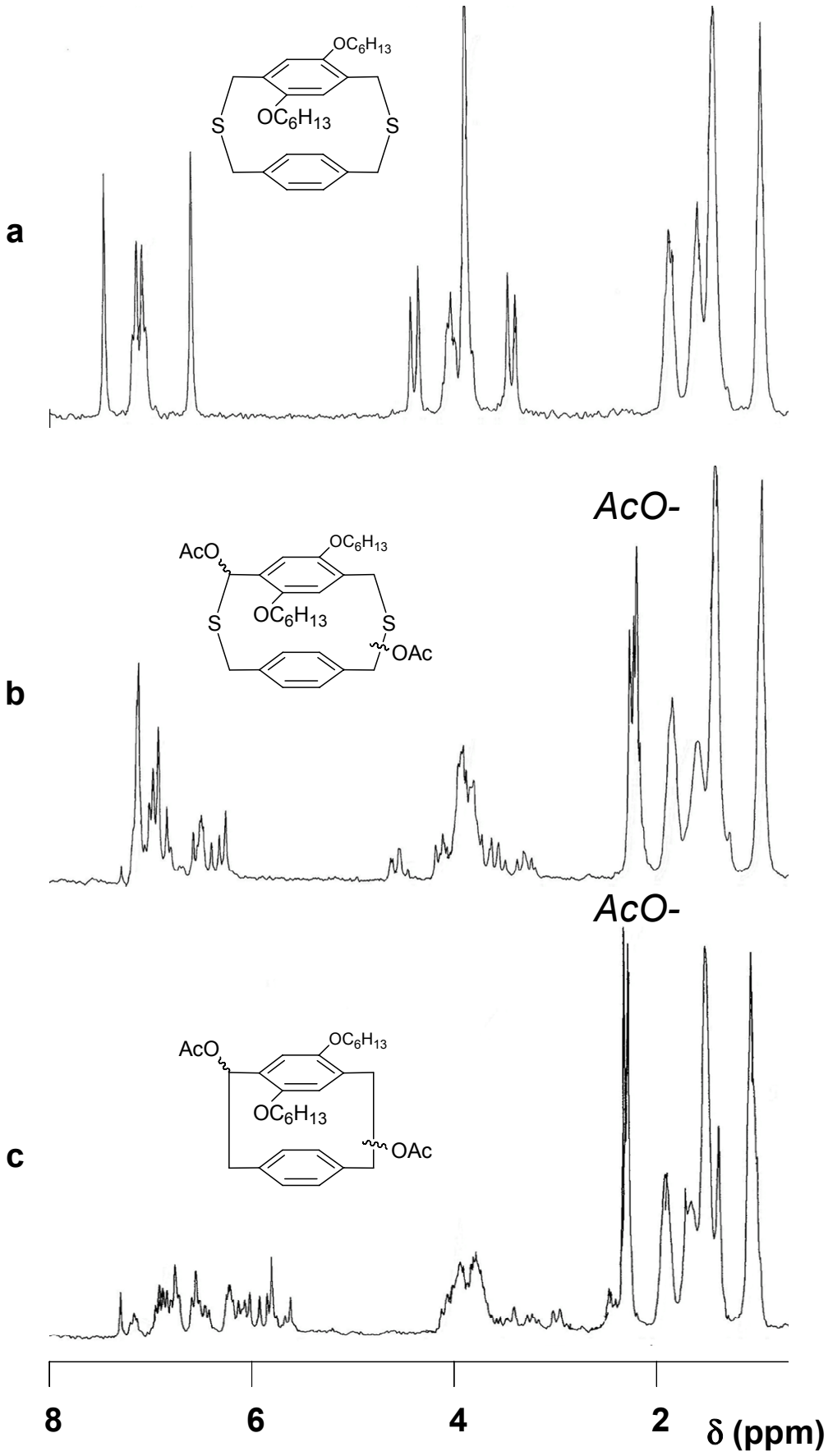


Figure S2. ^{1}H NMR (200 MHz, $CDCl_3$) of compounds: a) **13**; b) **17**; c) **20**.

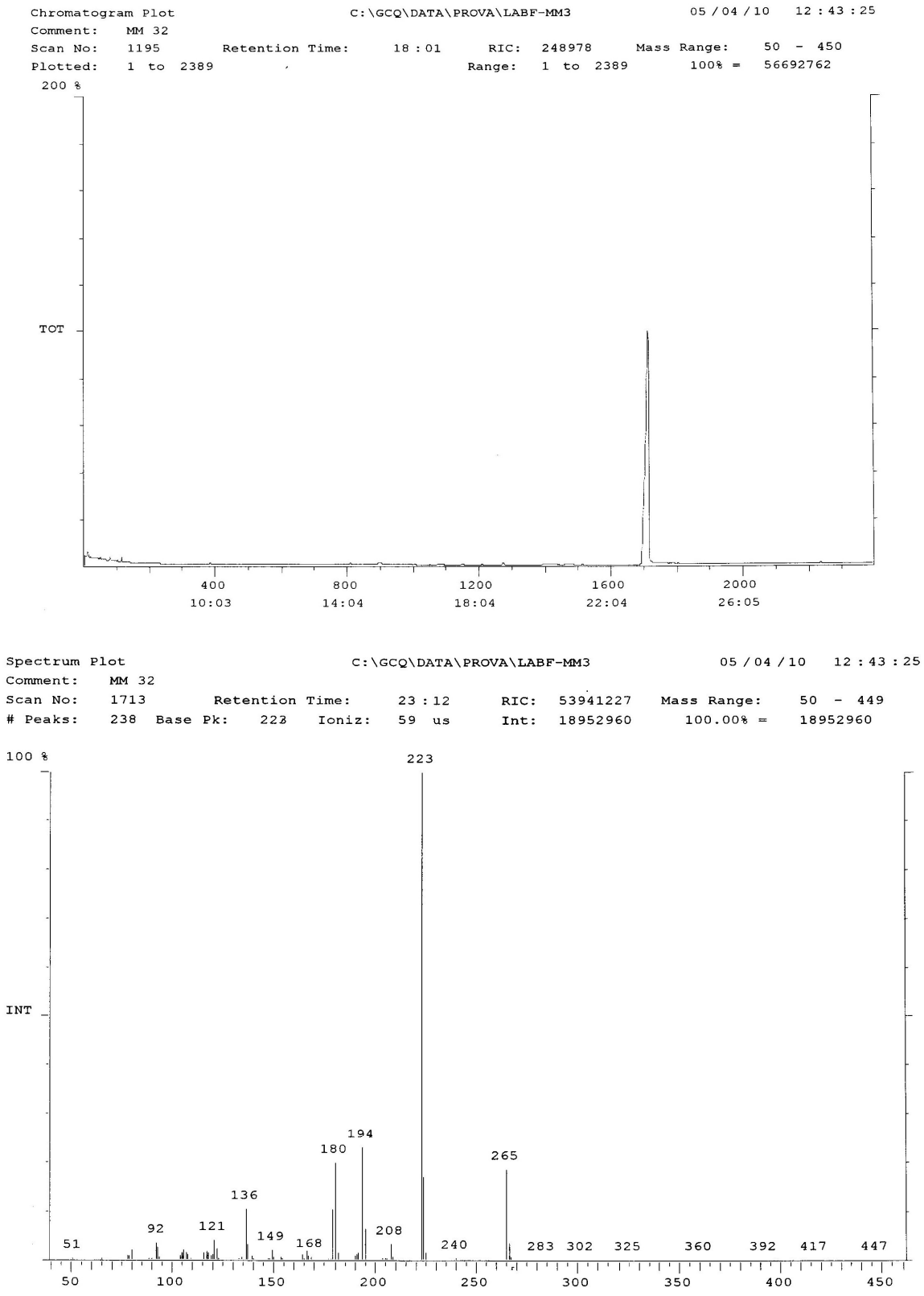


Figure S3. Gas chromatogram (top) and related mass spectrum for the peak at ca. 23 min for compound **18**.

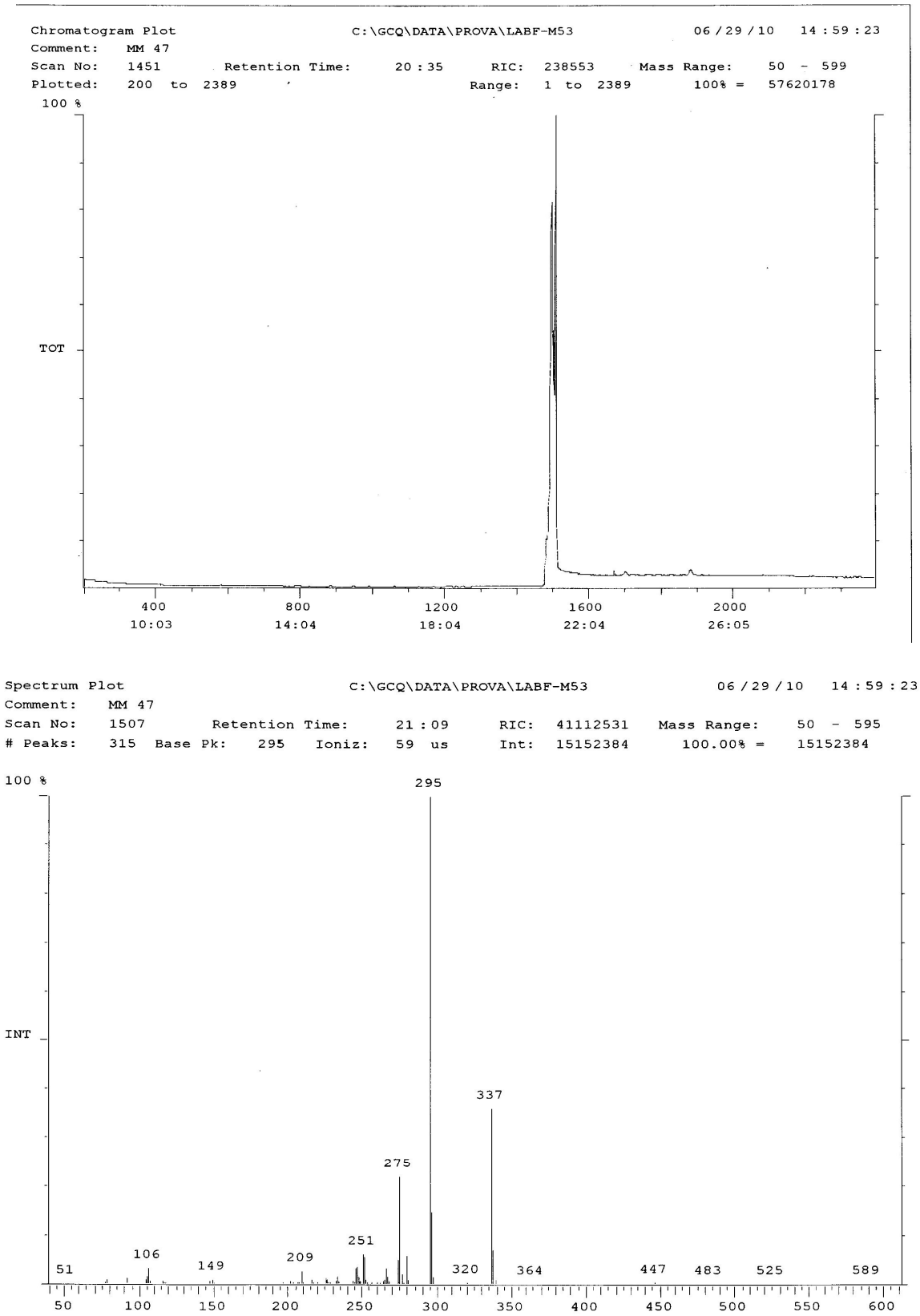


Figure S4. Gas chromatogram (top) and related mass spectrum for the peaks at 21-22 min for compound **19**. In all regions of the peaks the mass spectrum appears qualitatively the same.

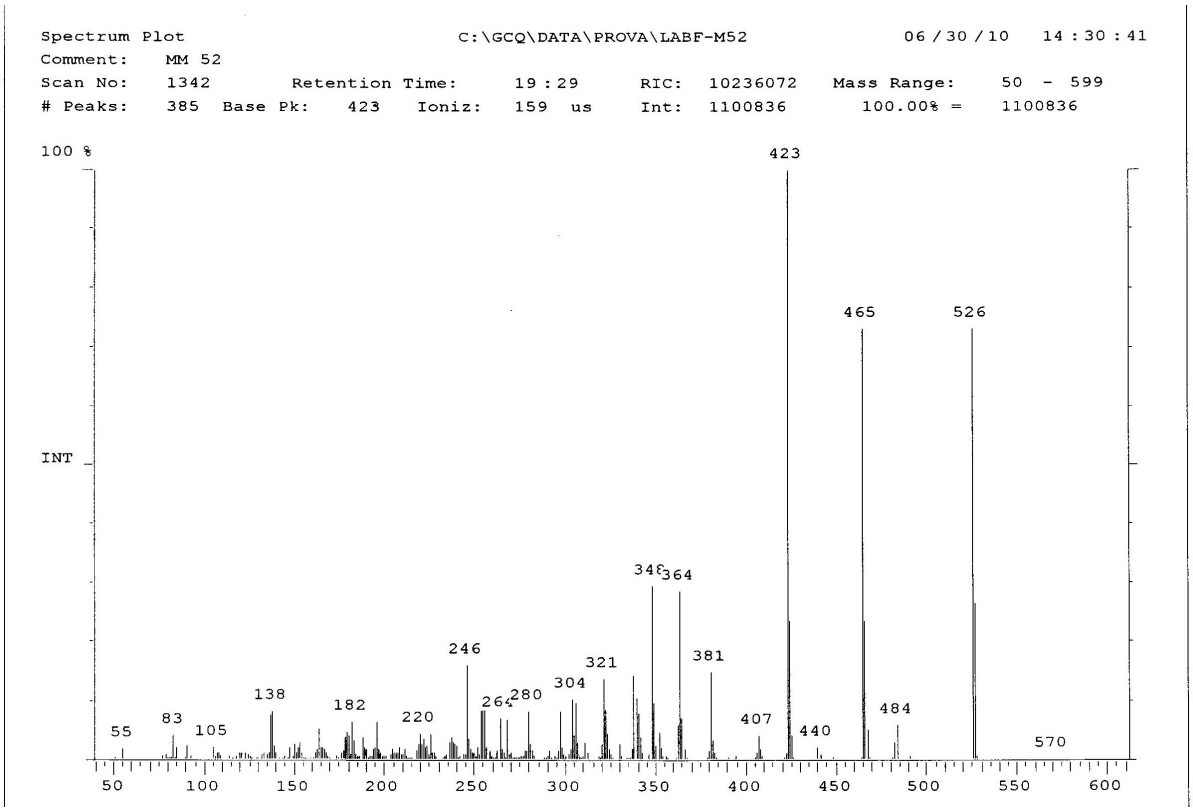


Figure S5. Mass spectrum for compound **20**.

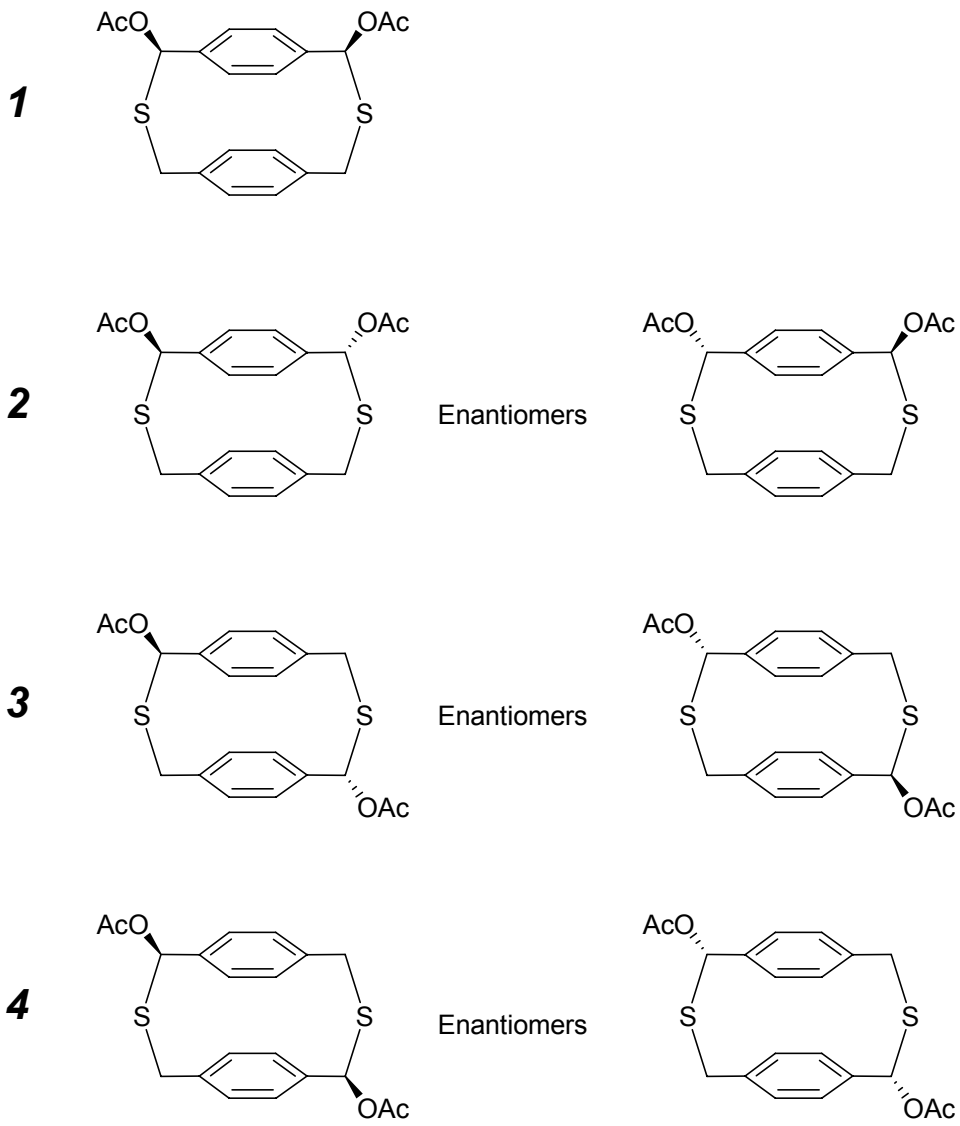


Figure S6. Representation of the stereo and regioisomeric forms obtainable for compound **15**.

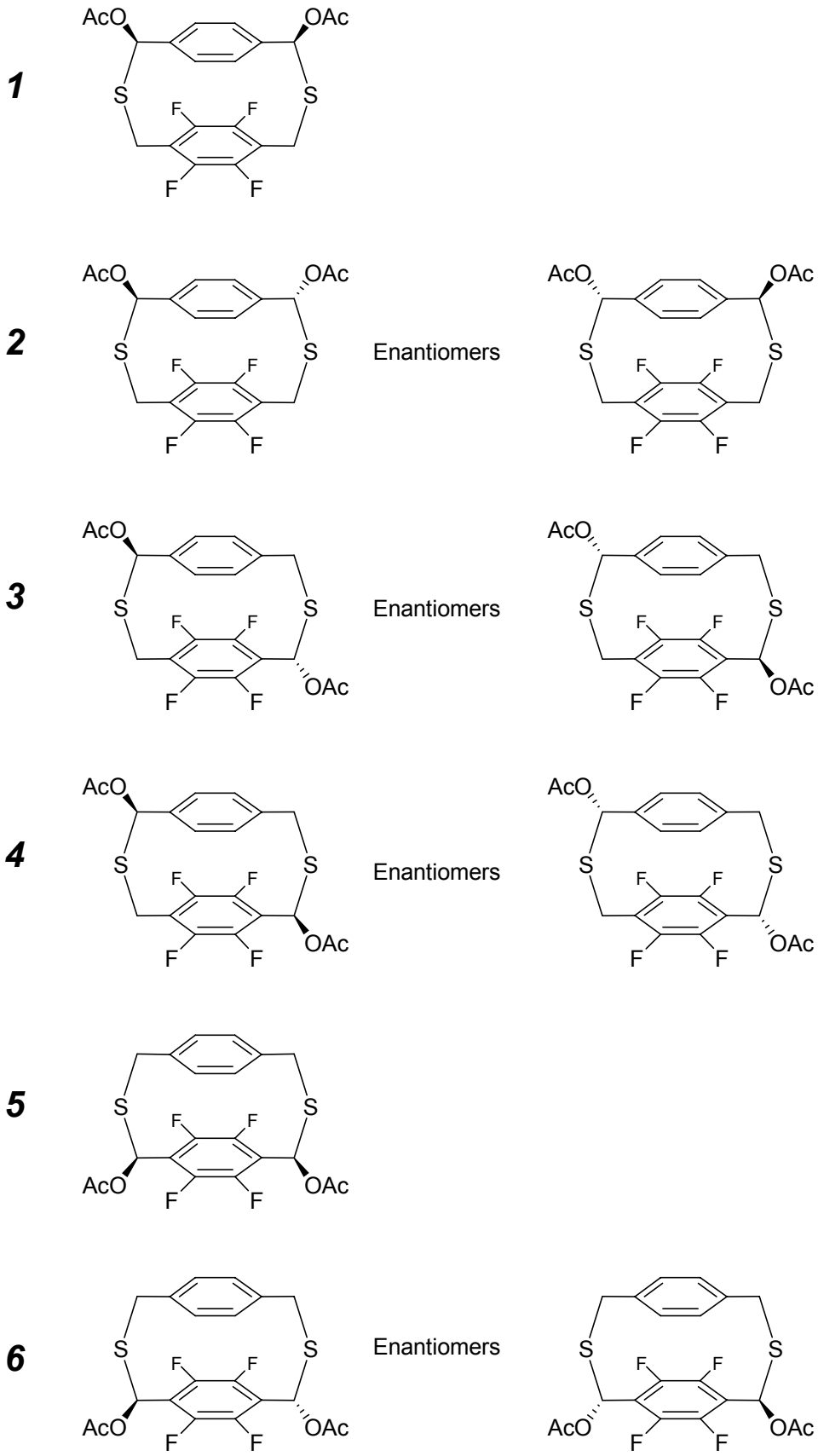


Figure S7. Representation of the stereo and regioisomeric forms obtainable for compound **16**.

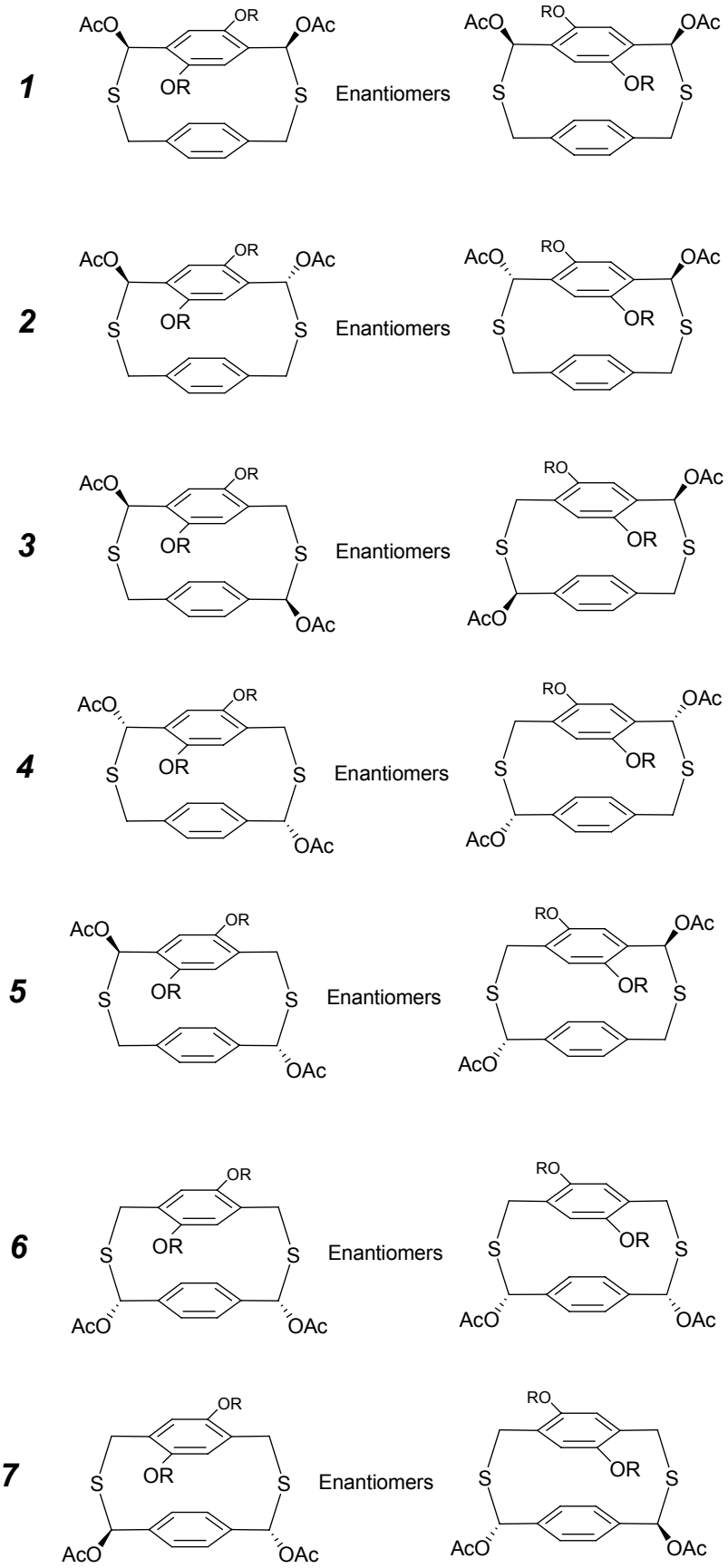
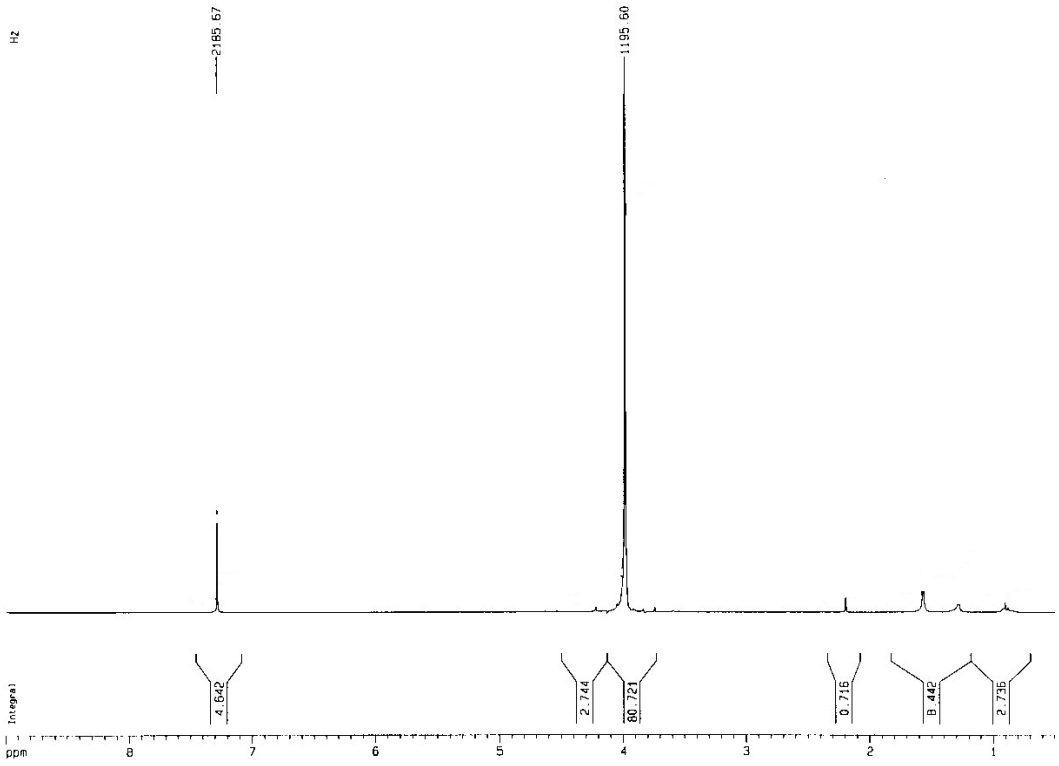
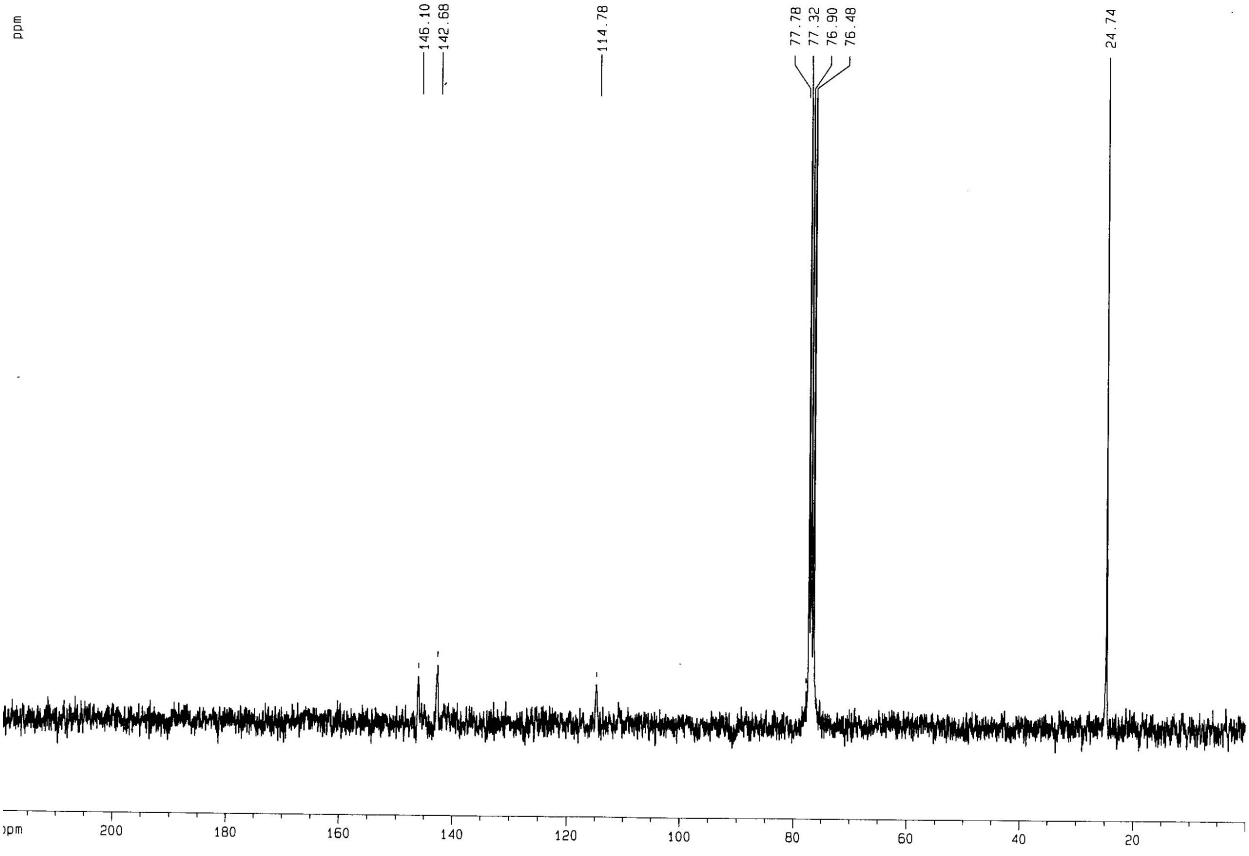


Figure S8. Representation of the stereo and regioisomeric forms obtainable for compound **17** ($R=C_6H_{13}$).

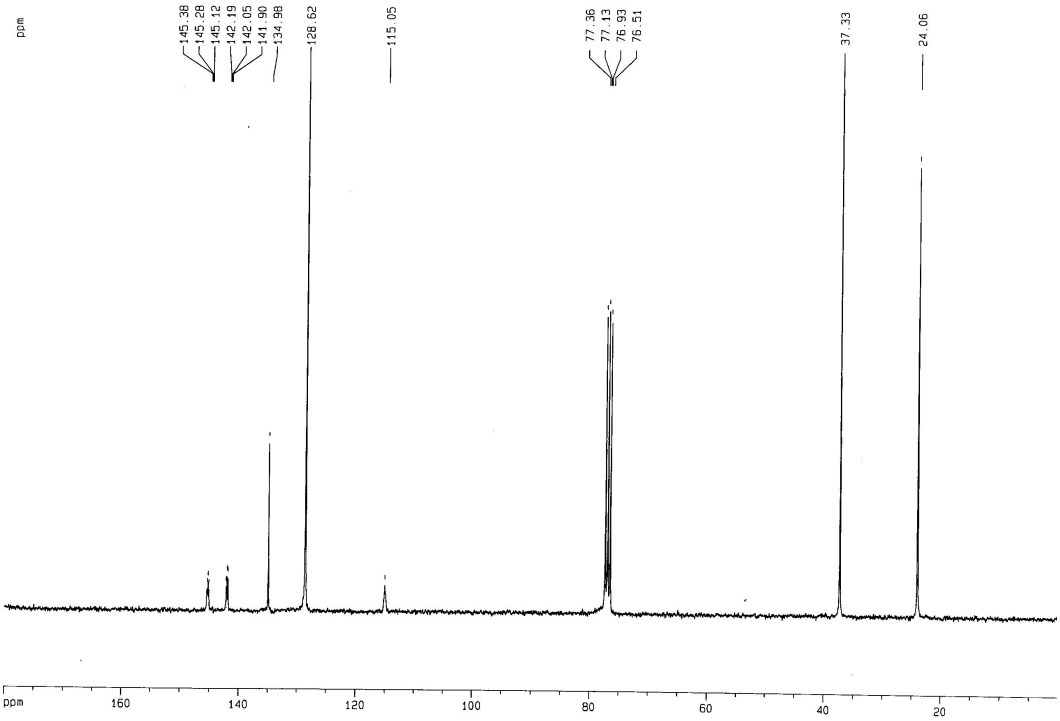
Additional NMR spectra and Mass spectra.

Compound 10.

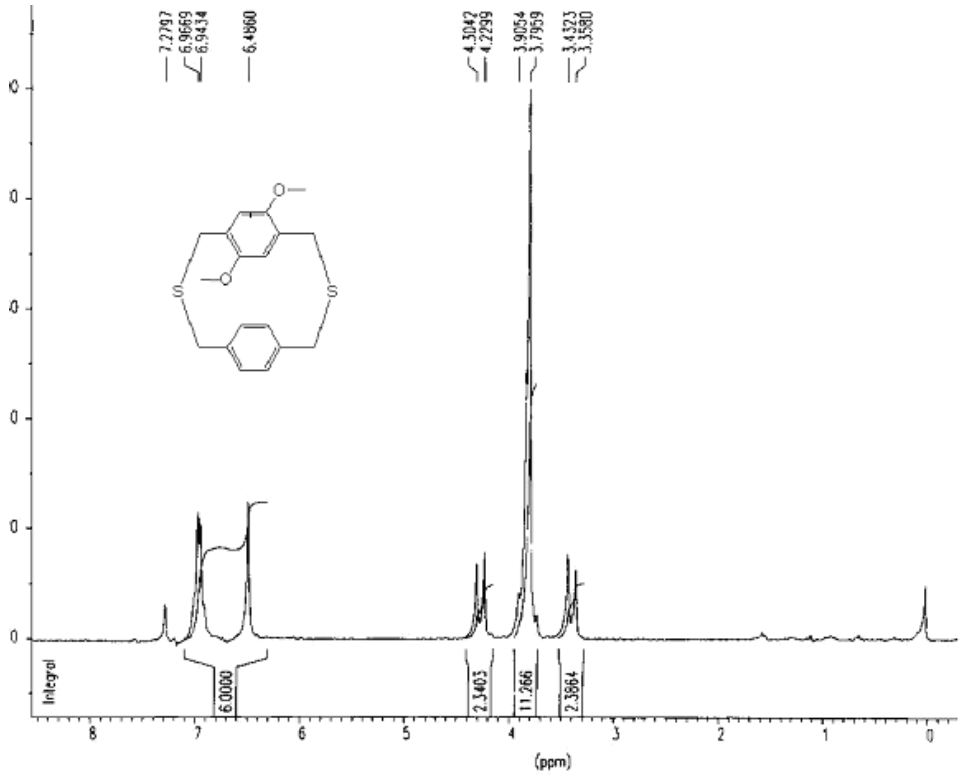




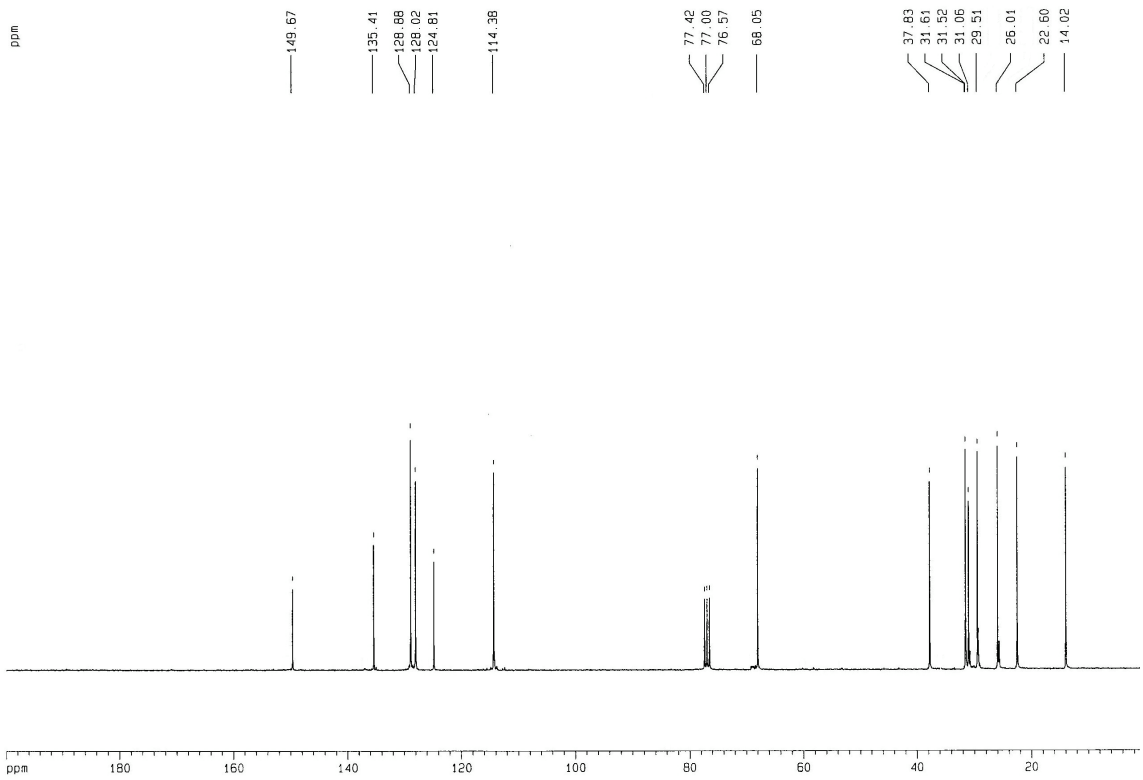
Compound 11.



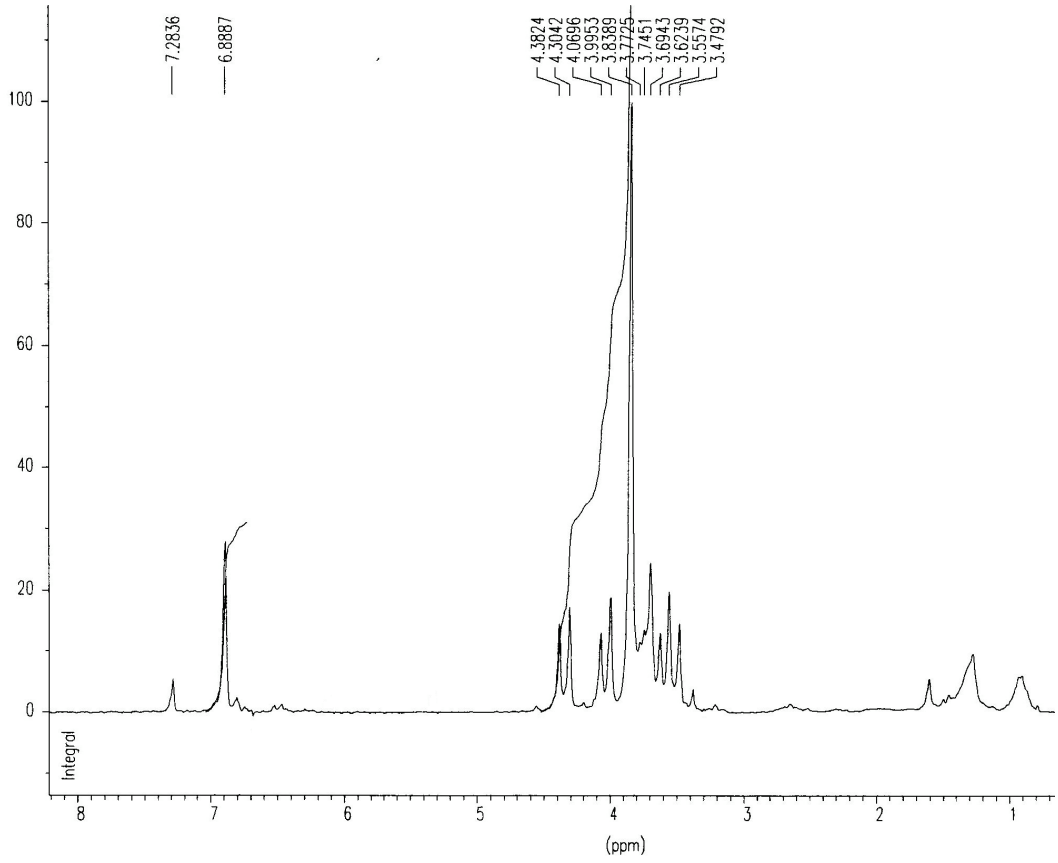
Compound 12.

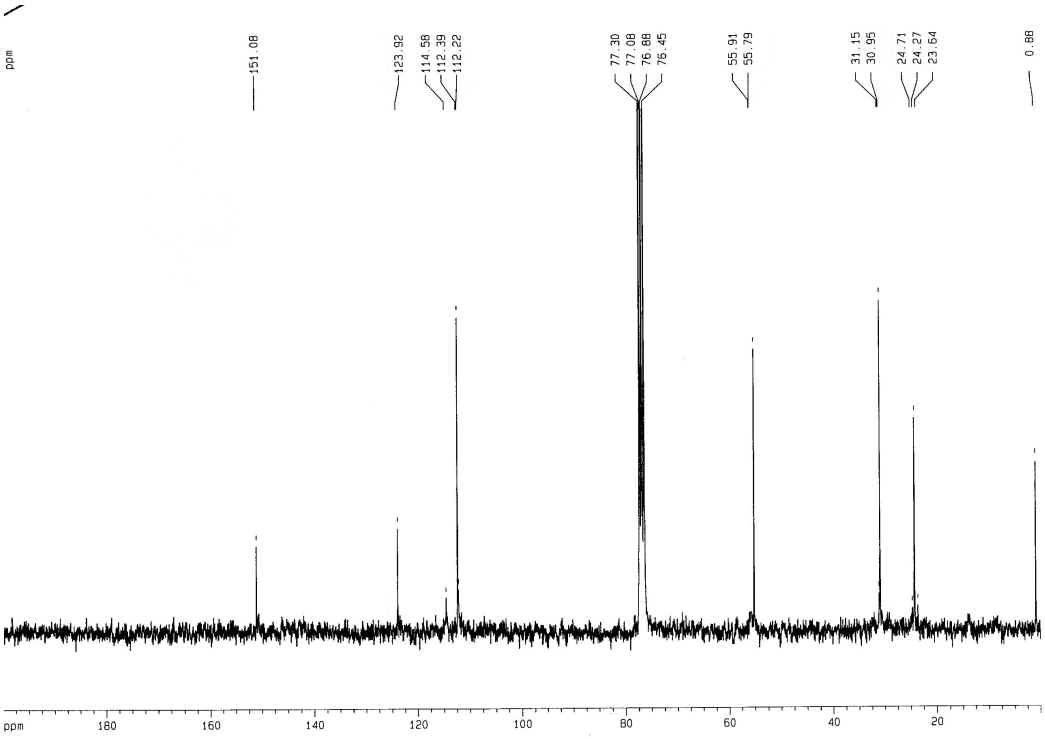


Compound 13.



Compound 14.

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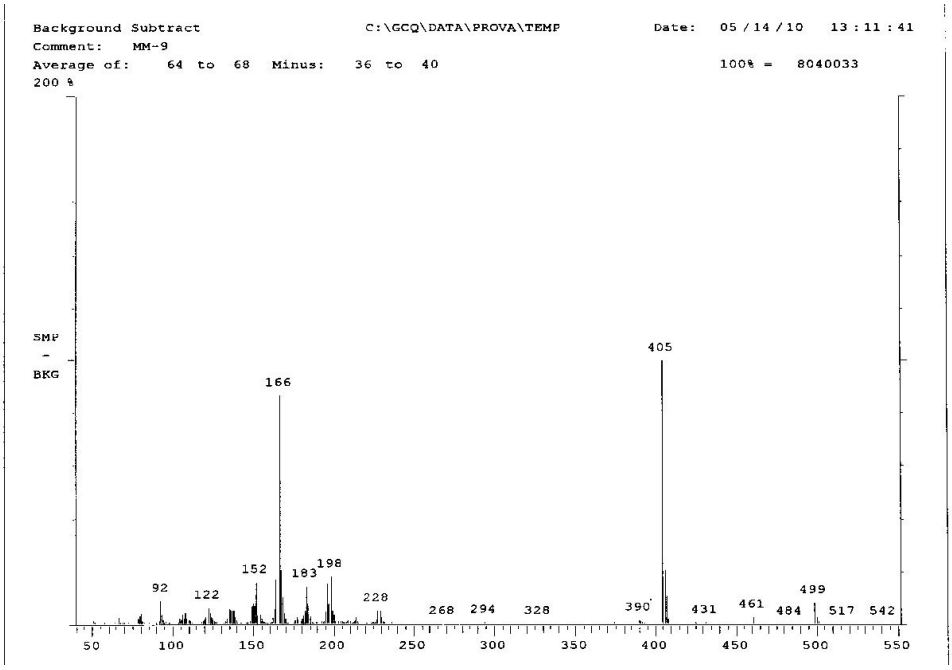
123.92
114.58
112.39
112.22
77.30
77.08
76.88
76.45
55.91
55.79
31.15
30.95
24.71
24.27
23.64
0.88
ppm
180
160
140
120
100
80
60
40
20


Background Subtract
C:\GCQ\DATA\PROVA\TEMP
Date: 05/14/10 13:11:41
Comment: MM-9
Average of: 64 to 68 Minus: 36 to 40
100% = 8040033
200 %
SMP
-
BKG
166
405
92
122
152
183
198
228
268
294
328
390
431
461
484
499
517
542
50
100
150
200
250
300
350
400
450
500
550

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