Synthesis of Cryptophane-223 Type Derivatives with dual functionalization

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S18: ^{1}H NMR (400 MHz) spectrum of compound **14** recorded in $CDCl_3$ at 298 K.

S19: ^{13}C NMR (100.6 MHz) spectrum of compound **14** recorded in $CDCl_3$ at 298 K.

S20: HSQC (400 MHz) spectrum of compound **14** recorded in $CDCl_3$ at 298 K.

S21:^{1}H NMR (400 MHz) spectrum of compound **15** recorded in $CDCl_3$ at 298 K.

S22: ^{13}C NMR (100.6 MHz) spectrum of compound **15** recorded in $CDCl_3$ at 298 K.

S23: HSQC (400 MHz) spectrum of compound **15** recorded in $CDCl_3$ at 298 K.

S24: ^{1}H NMR (400 MHz) spectrum of compound **18** recorded in $CDCl_3$ at 298 K.

S25: ^{13}C NMR (100.6 MHz) spectrum of compound **18** recorded in $CDCl_3$ at 298 K.

S26: HSQC (400 MHz) spectrum of compound **18** recorded in $CDCl_3$ at 298 K.

S27: ^{1}H NMR (400 MHz) spectrum of compound **19** recorded in $CDCl_3$ at 298 K.

S28: ^{13}C NMR (100.6 MHz) spectrum of compound **19** recorded in $CDCl_3$ at 298 K.

S29: HSQC (400 MHz) spectrum of compound **19** recorded in $CDCl_3$ at 298 K.

S30: ^{1}H NMR (400 MHz) spectrum of compound **21** recorded in $CDCl_3$ at 298 K.

S31: ^{13}C NMR (100.6 MHz) spectrum of compound **21** recorded in $CDCl_3$ at 298 K.

S32: HSQC (400 MHz) spectrum of compound **21** recorded in $CDCl_3$ at 298 K.

S33: ^{1}H NMR (400 MHz) spectrum of compound **2** recorded in DMSO-d_6 at 298 K.

S34: ^{13}C NMR (100.6 MHz) spectrum of compound **2** recorded in DMSO-d_6 at 298 K.

S35: HSQC (400 MHz) spectrum of compound **2** recorded in DMSO-d_6 at 298 K.

S36: COSY (400 MHz) spectrum of compound **2** recorded in DMSO-d_6 at 298 K.

S37: ^{1}H NMR (400 MHz) spectrum of compound **23** recorded in $CDCl_3$ at 298 K.

S38: ^{13}C NMR (100.6 MHz) spectrum of compound **23** recorded in $CDCl_3$ at 298 K.

S39: HSQC (400 MHz) spectrum of compound **23** recorded in $CDCl_3$ at 298 K.

S40: ORTEP representation of compound **9** (hydrogen atoms and solvent molecule were omitted for clarity. The displacement ellipsoids were plotted at 30% probability level).

S41: Calorimetric titration of compound **2** in H_2O/TRIS (20 mM; pH = 7.6). The solution host (c = 0.08 mM) was placed into the calorimeter cell (1.4 mL) and 28 successive aliquots (10 μL) of Ni^{2+} solution (c = 1.0 mM) were added at 3 min intervals.

S42: Calorimetric titration of Cryptophane-222 hexacarboxylate in H_2O/TRIS (20 mM; pH = 7.0). The solution host (c = 0.08 mM) was placed into the calorimeter cell (1.4 mL) and 28 successive aliquots (10 μL) of Ni^{2+} solution (c = 1.0 mM) were added at 3 min intervals.

S43: Hyperpolarized 129-xenon spectra of compound **2** in TRIS buffer (20 mM, pH = 7.5). a) in absence of Zn^{2+} (green spectrum). b) in presence of 1 equiv. of Zn^{2+} (blue spectrum). c) in presence of 5 equiv. of Zn^{2+} (red spectrum). Spectra recorded at 25°C.

S44: hyperpolarized ^{129}Xe NMR spectrum of compound **10** recorded at 298 K in $C_2D_2Cl_4$.

Table S1: Crystallographic data of cryptophane **9**.

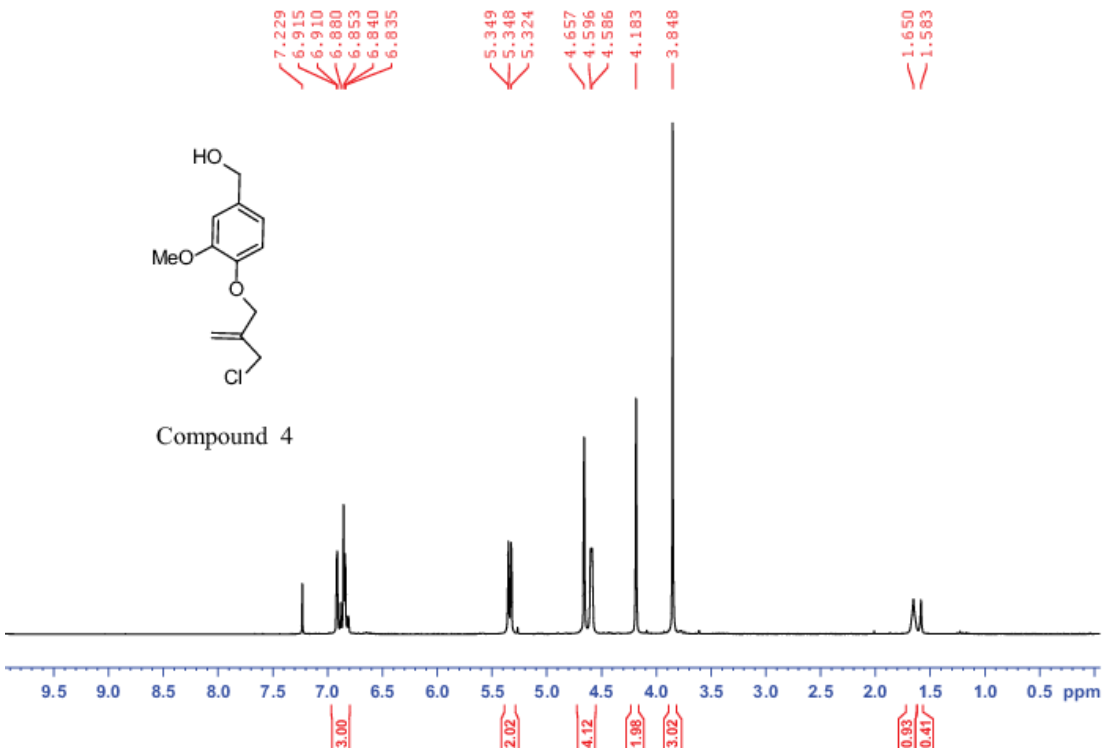

Figure S1: ^{1}H NMR (400 MHz) spectrum of compound **4** recorded in $CDCl_3$ at 298 K.

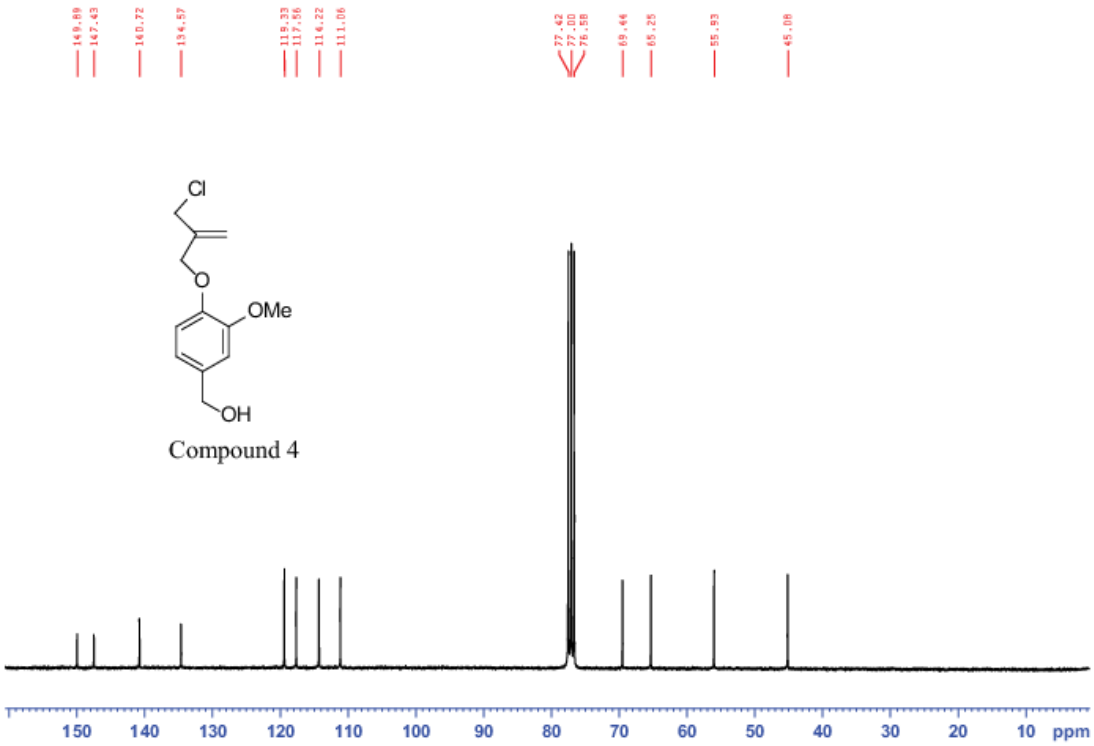

Figure S2: ^{13}C NMR (100.6 MHz) spectrum of compound **4** recorded in $CDCl_3$ at 298 K.

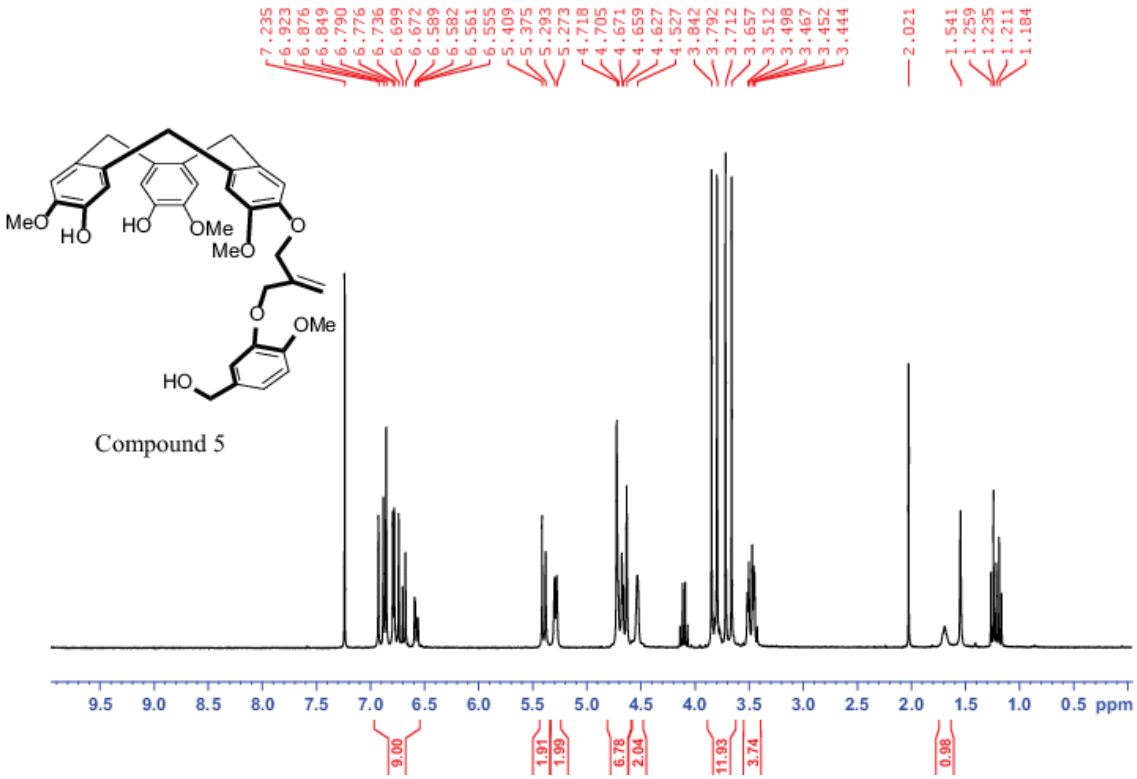

Figure S3: ^{1}H NMR (400 MHz) spectrum of CTB **5** recorded in $CDCl_3$ at 298 K.

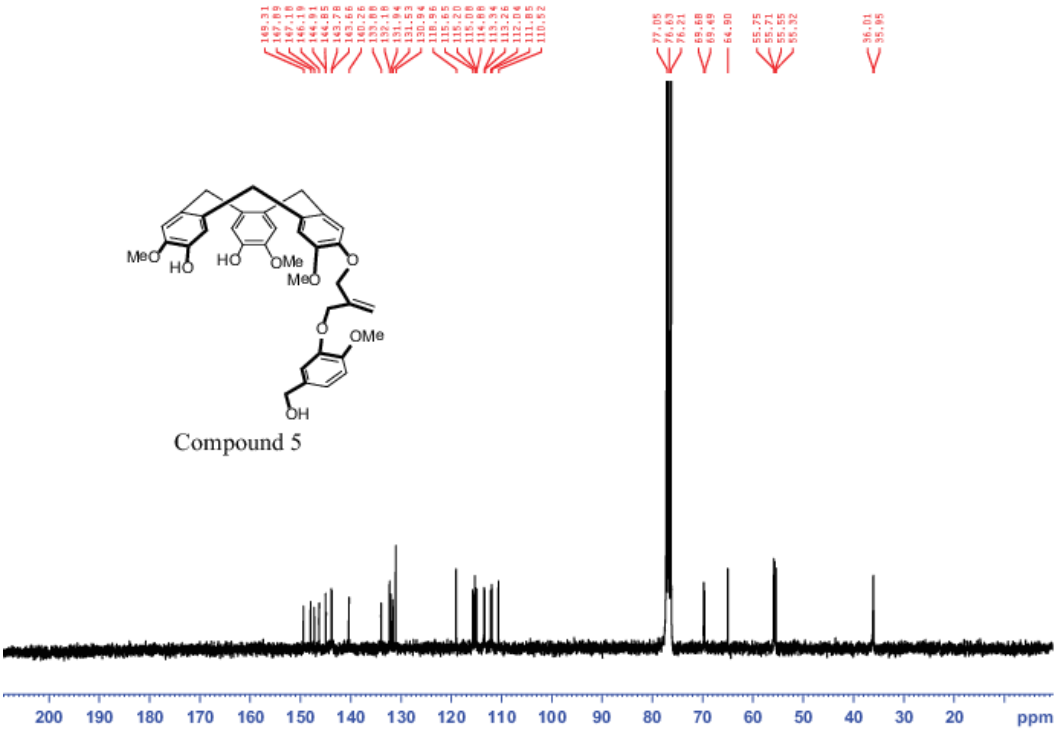

Figure S4: ^{13}C NMR (100.6 MHz) spectrum of CTB **5** recorded in $CDCl_3$ at 298 K.

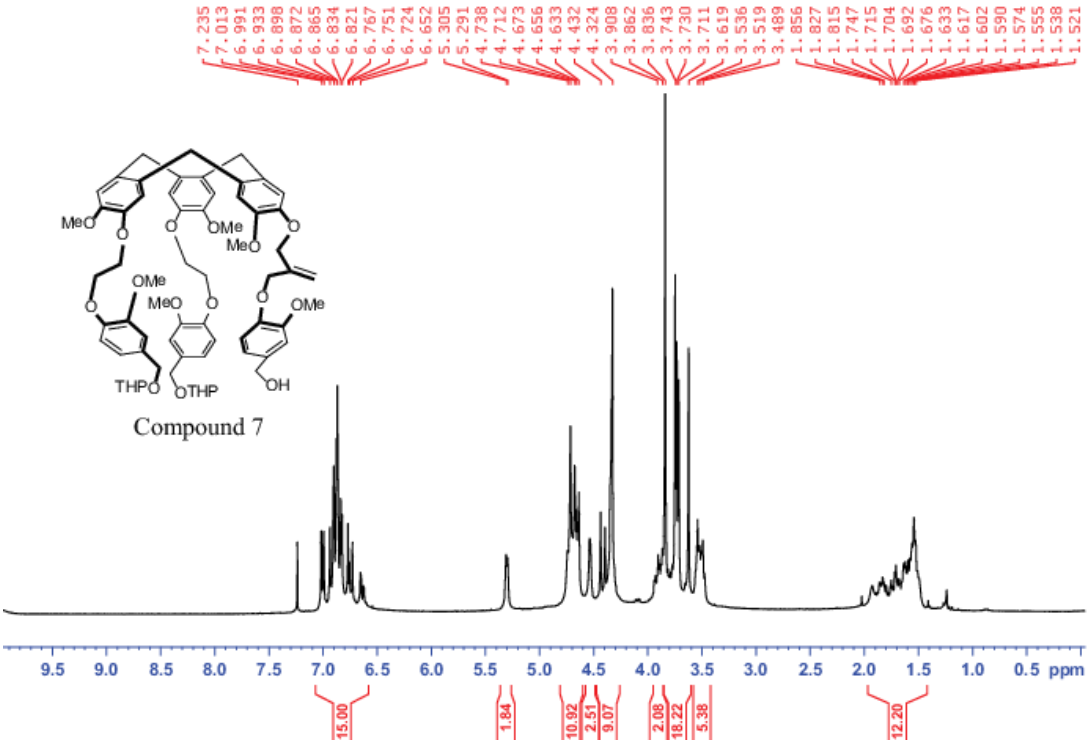

Figure S5: ^{1}H NMR (400 MHz) spectrum of CTB **7** recorded in $CDCl_3$ at 298 K.

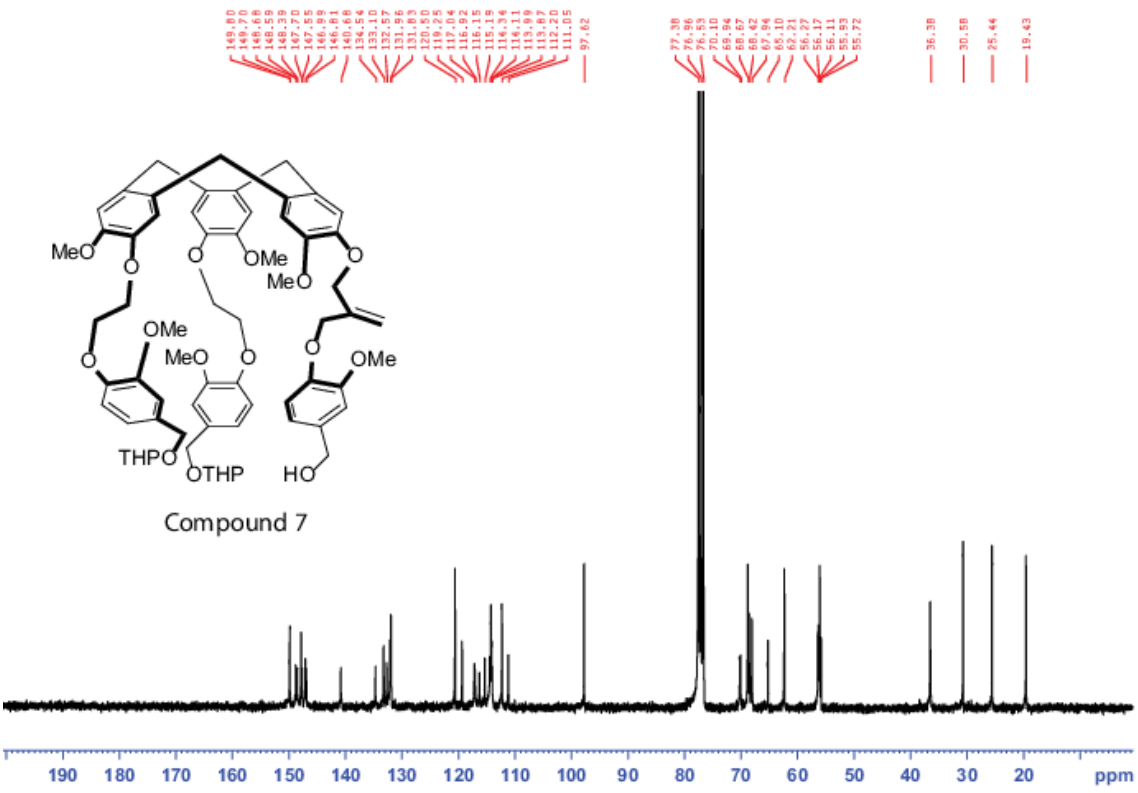

Figure S6: ^{13}C NMR (100.6 MHz) spectrum of CTB **7** recorded in $CDCl_3$ at 298 K.

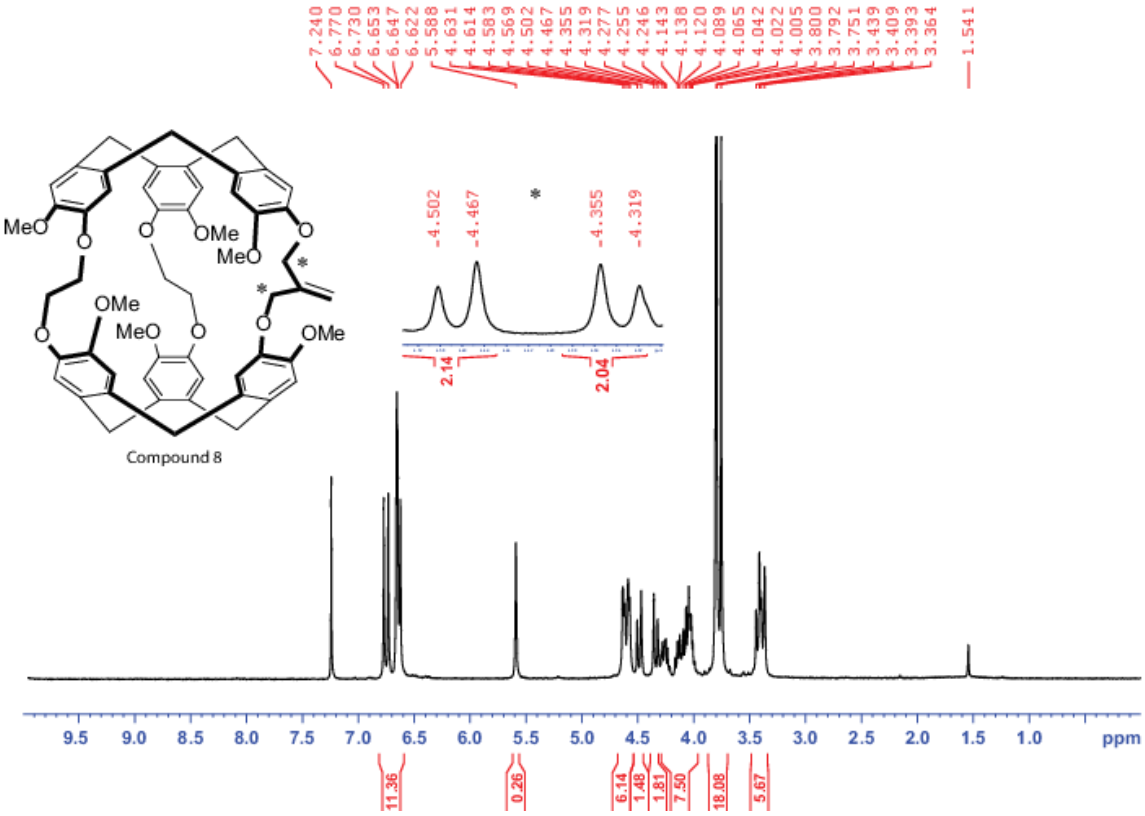

Figure S7: ^{1}H NMR (400 MHz) spectrum of compound **8** recorded in $CDCl_3$ at 298 K.

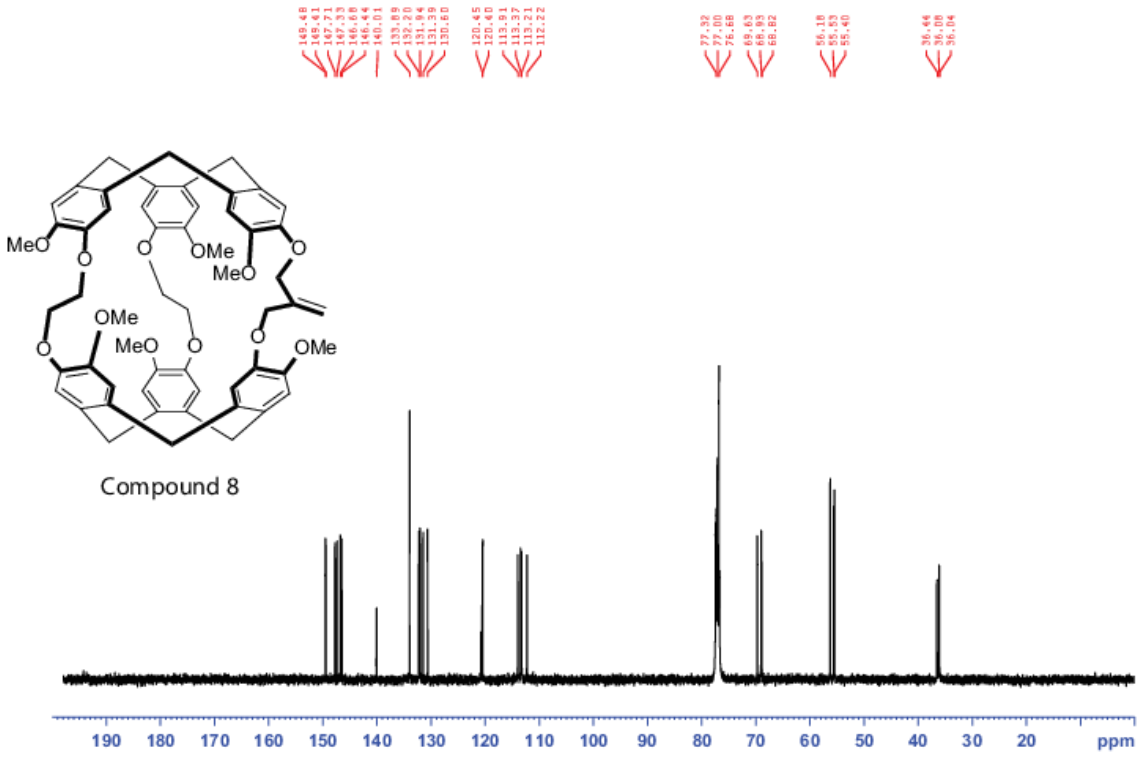

Figure S8: ^{13}C NMR (100.6 MHz) spectrum of compound **8** recorded in $CDCl_3$ at 298 K.

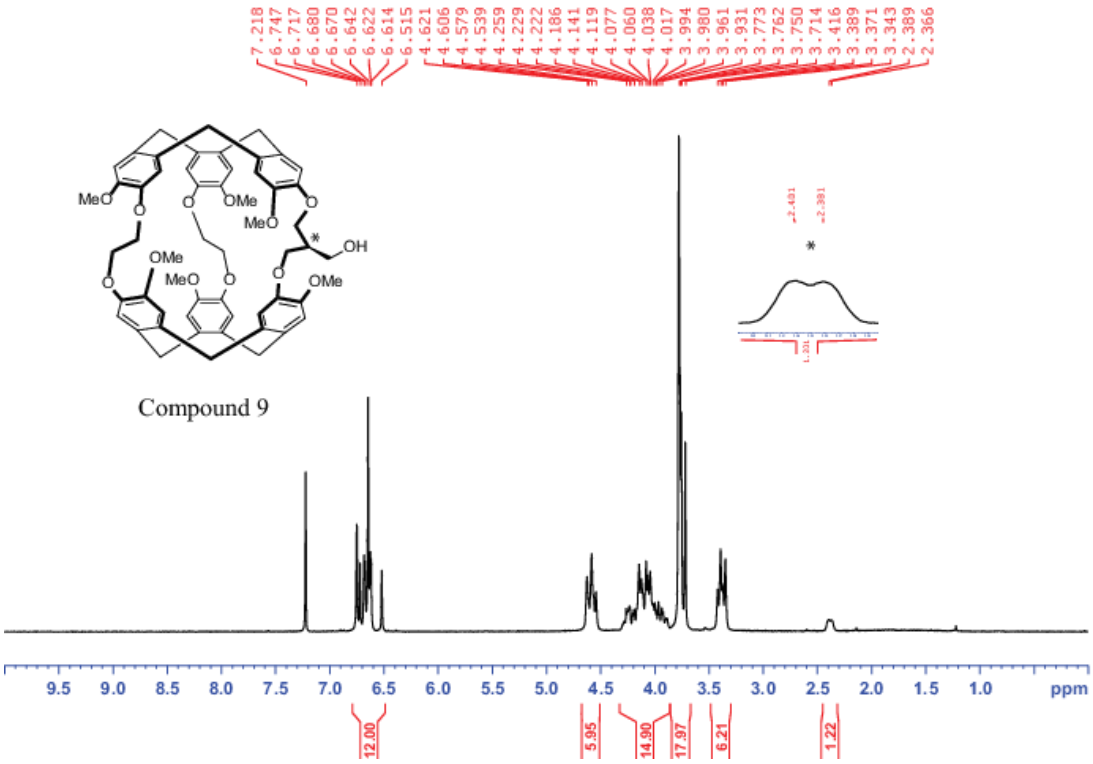

Figure S9: ^{1}H NMR (400 MHz) spectrum of compound **9** recorded in $CDCl_3$ at 298 K.

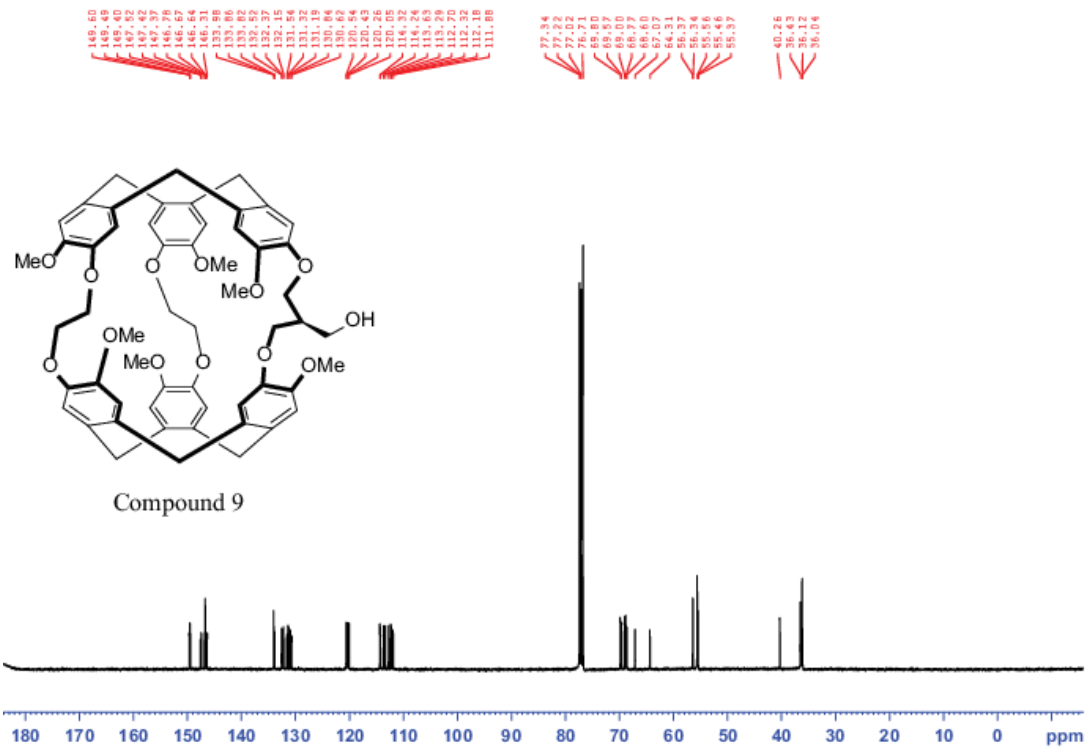

Figure S10: ^{13}C NMR (100.6 MHz) spectrum of compound **9** recorded in $CDCl_3$ at 298 K.

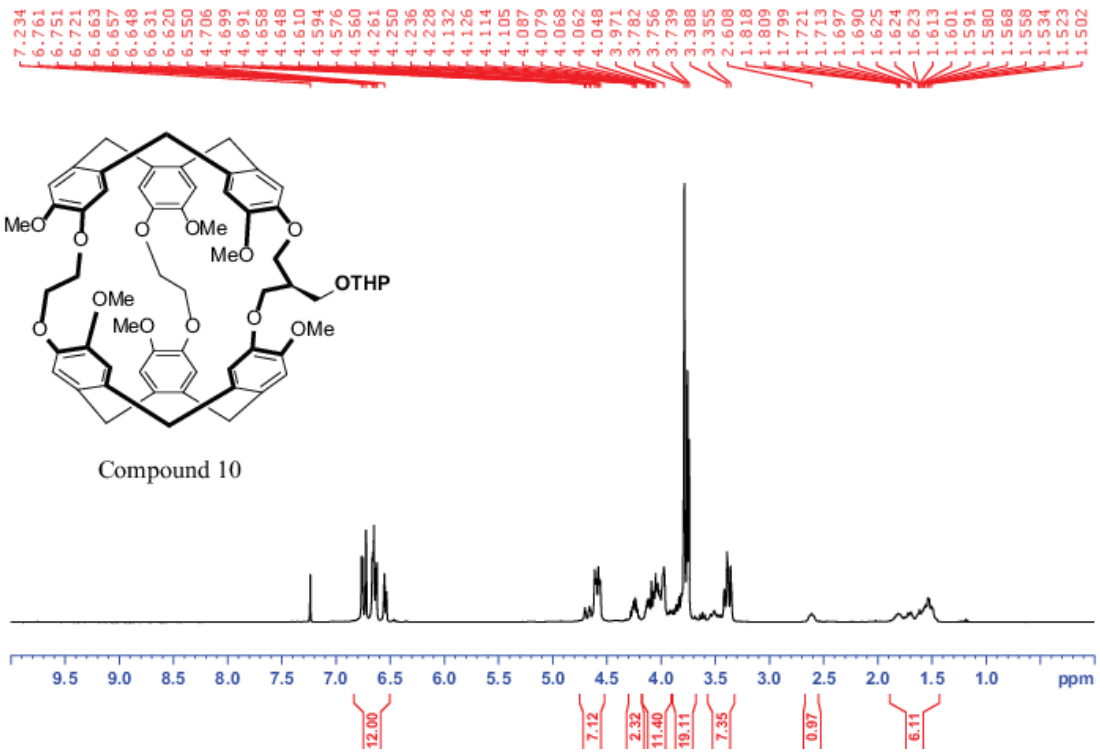

Figure S11: ^{1}H NMR (400 MHz) spectrum of compound **10** recorded in $CDCl_3$ at 298 K.

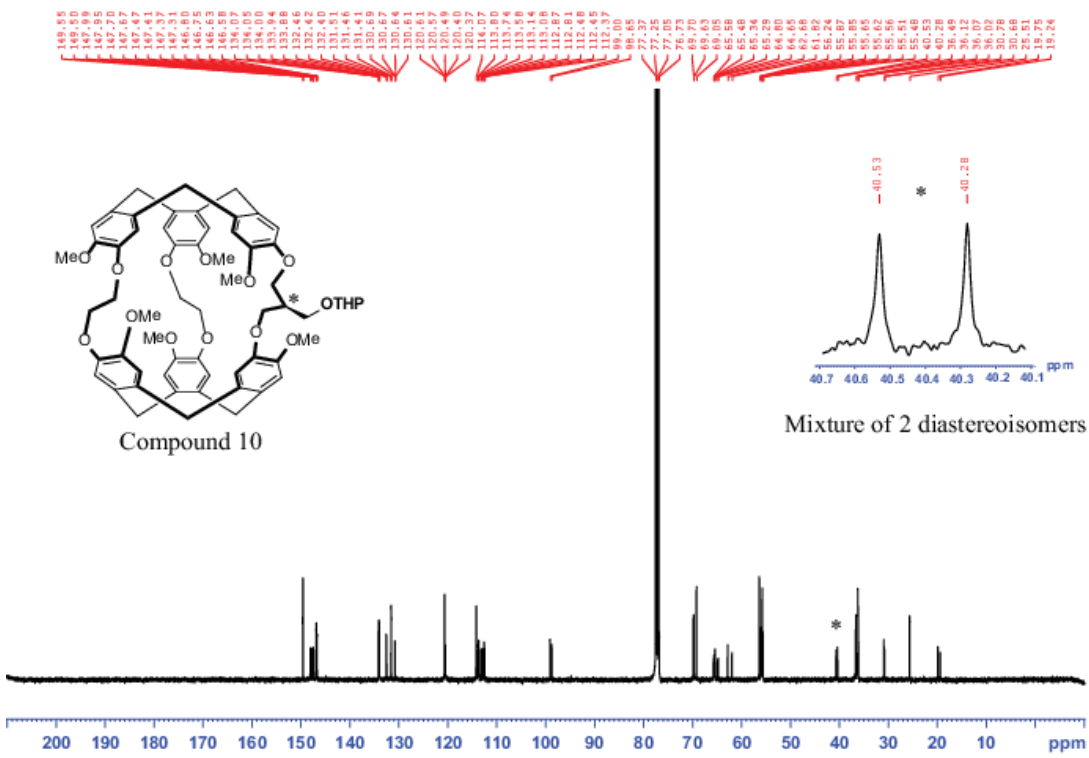

Figure S12: ^{13}C NMR (100.6 MHz) spectrum of compound **10** recorded in $CDCl_3$ at 298 K.

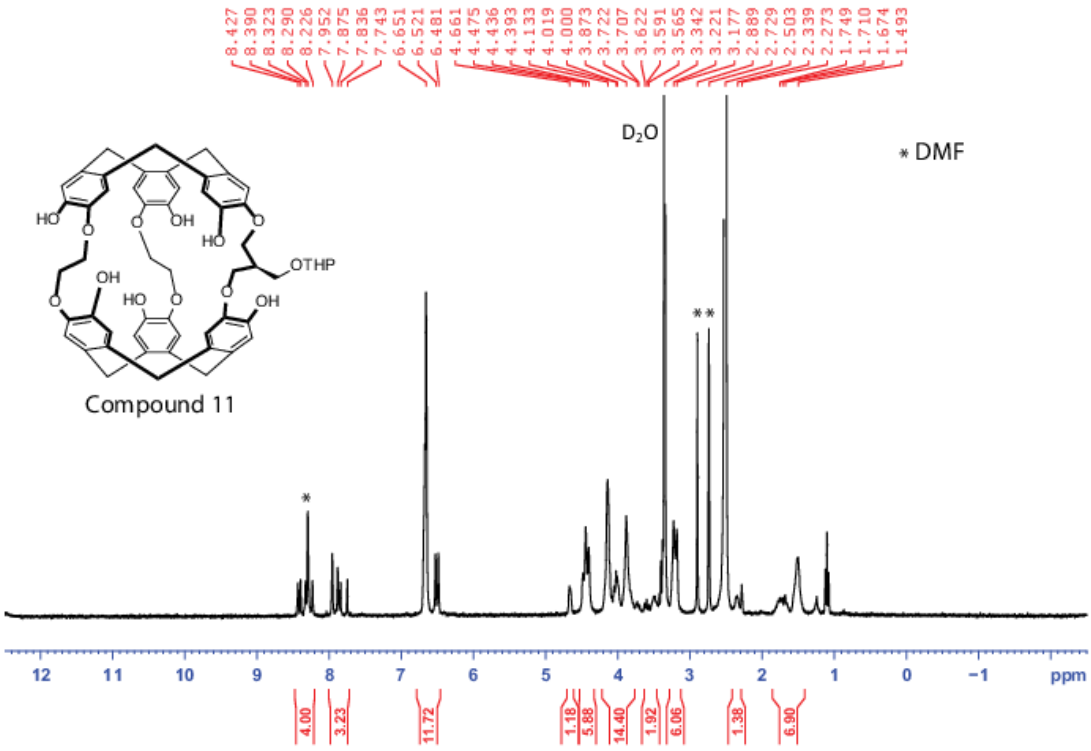

Figure S13: ^{1}H NMR (400 MHz) spectrum of compound **11** recorded in DMSO-d_6 at 298 K.

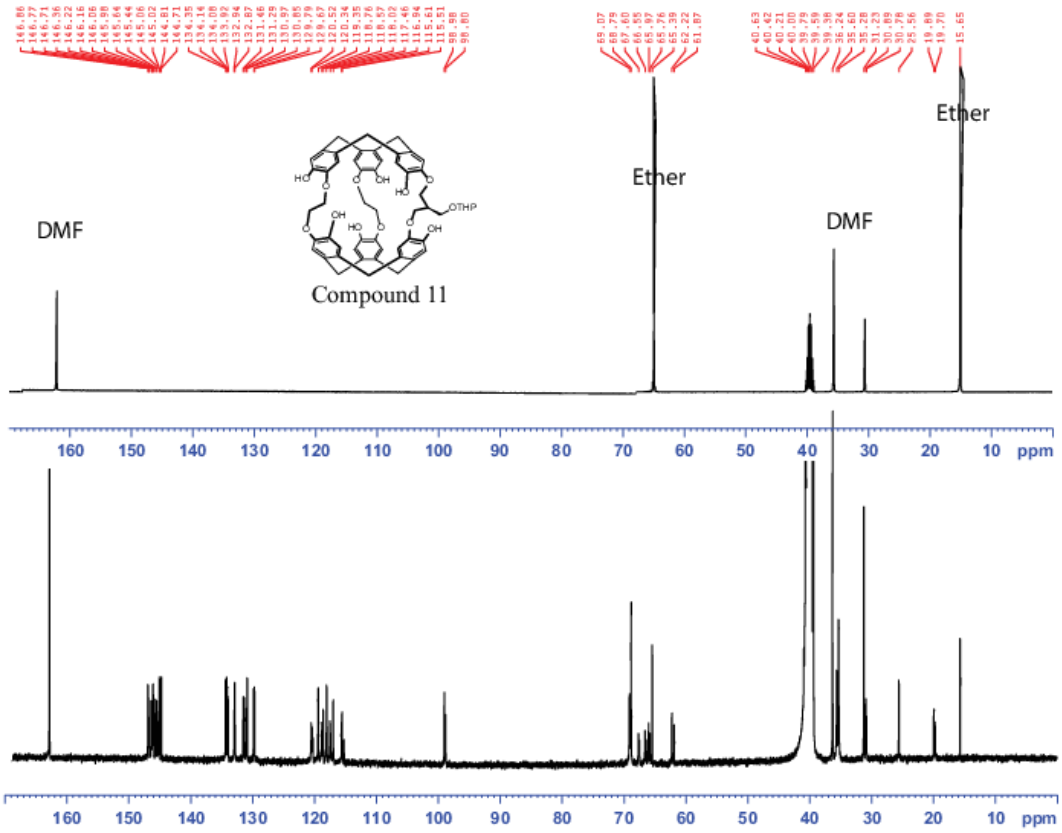

Figure S14: ^{13}C NMR (100.6 MHz) spectrum of compound **11** recorded in DMSO-d_6 at 298K.

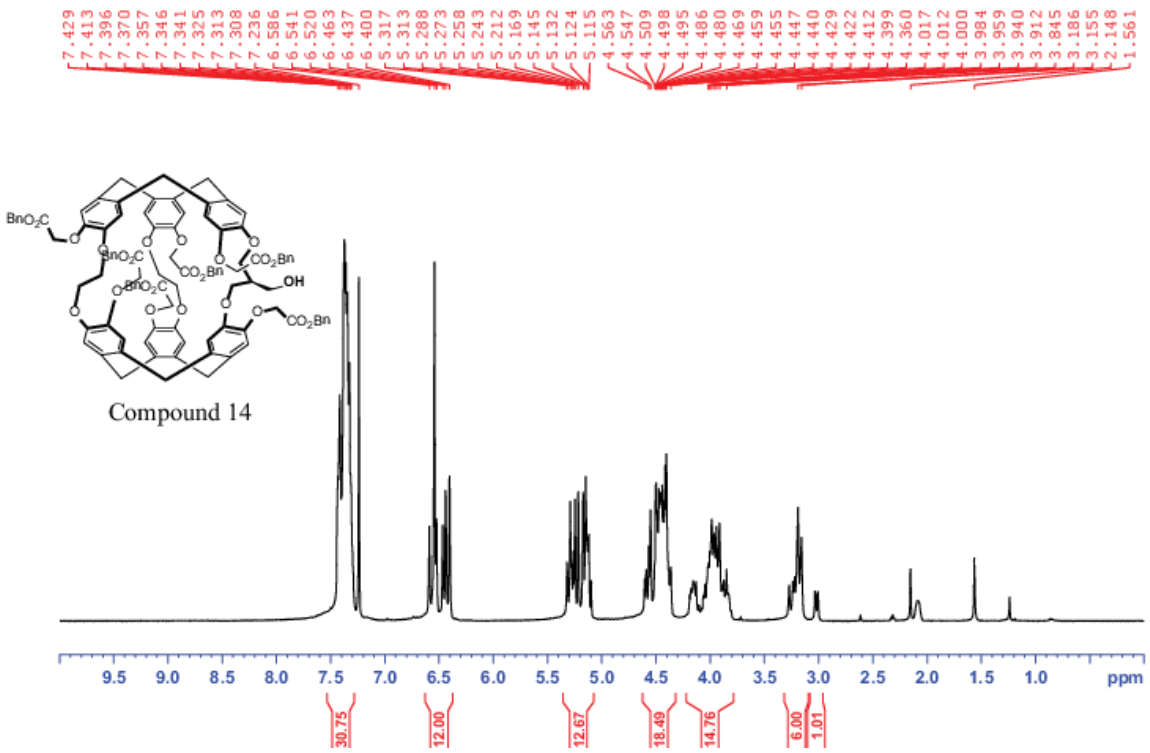

Figure S15: ^{1}H NMR (400 MHz) spectrum of compound **14** recorded in $CDCl_3$ at 298 K.

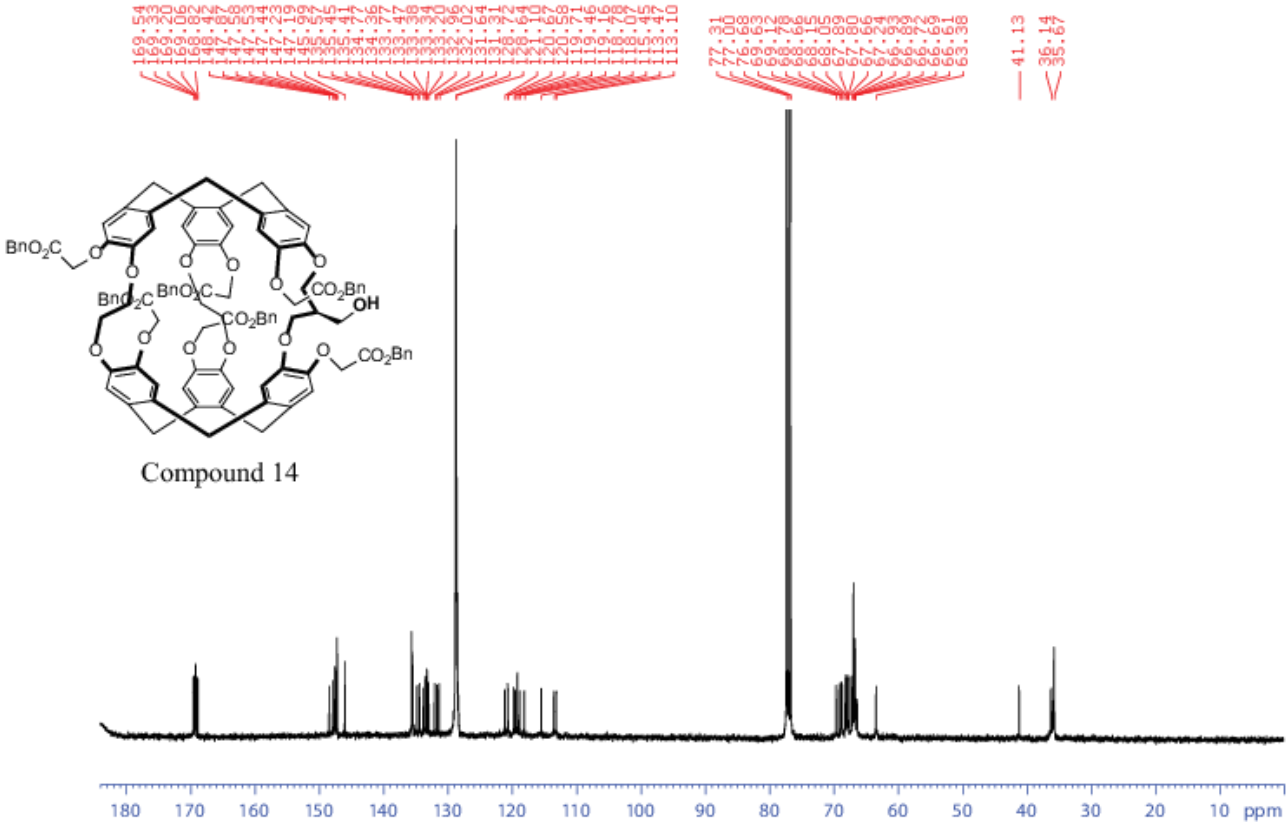

Figure S16: ^{13}C NMR (100.6 MHz) spectrum of compound **14** recorded in $CDCl_3$ at 298 K.

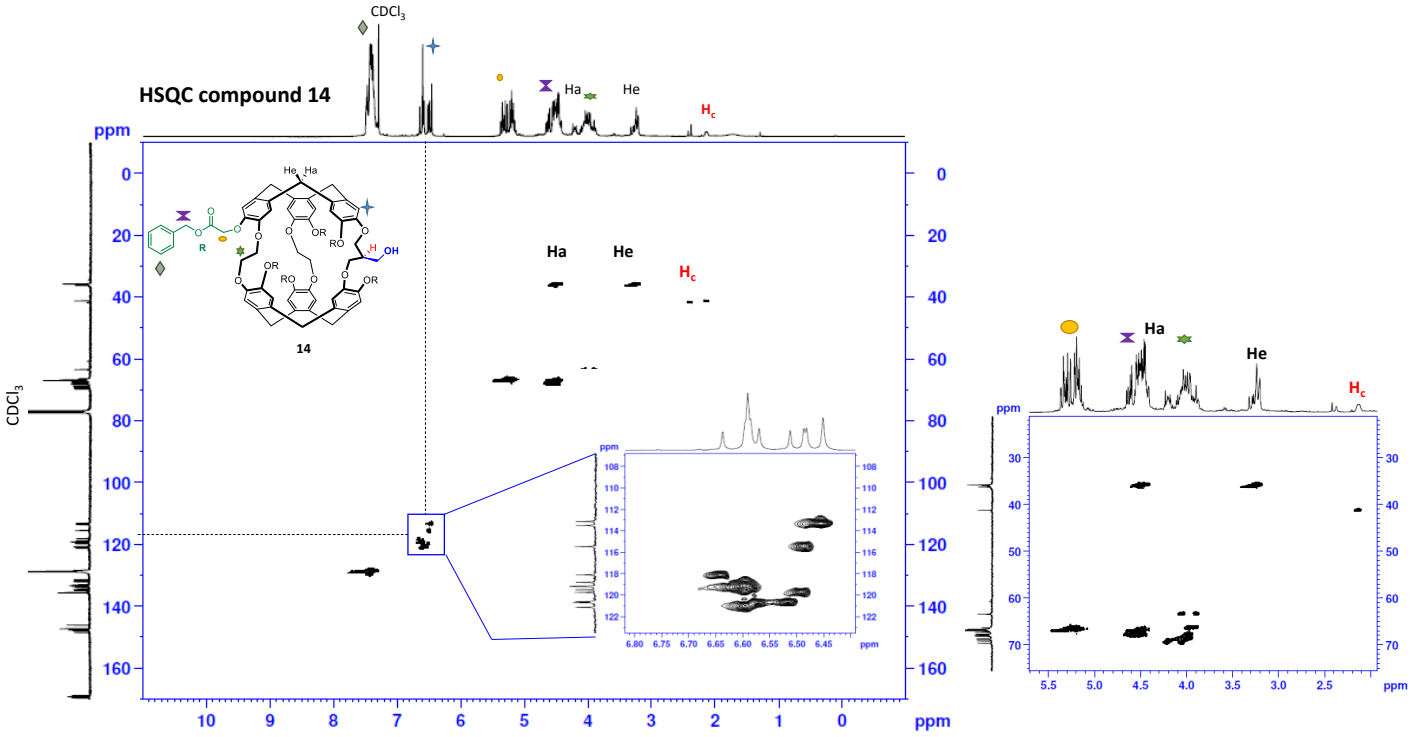

Figure S17: HSQC (400 MHz) spectrum of compound **14** recorded in $CDCl_3$ at 298 K.

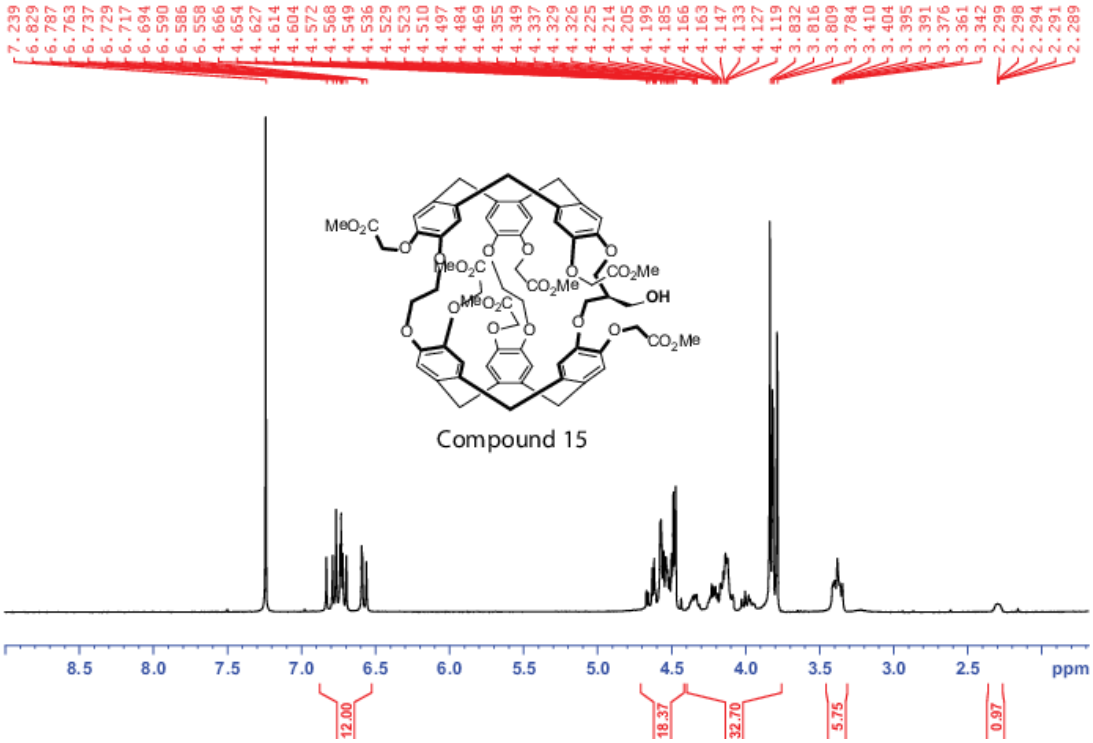

Figure S18: ^{1}H NMR (400 MHz) spectrum of compound **15** recorded in $CDCl_3$ at 298 K.

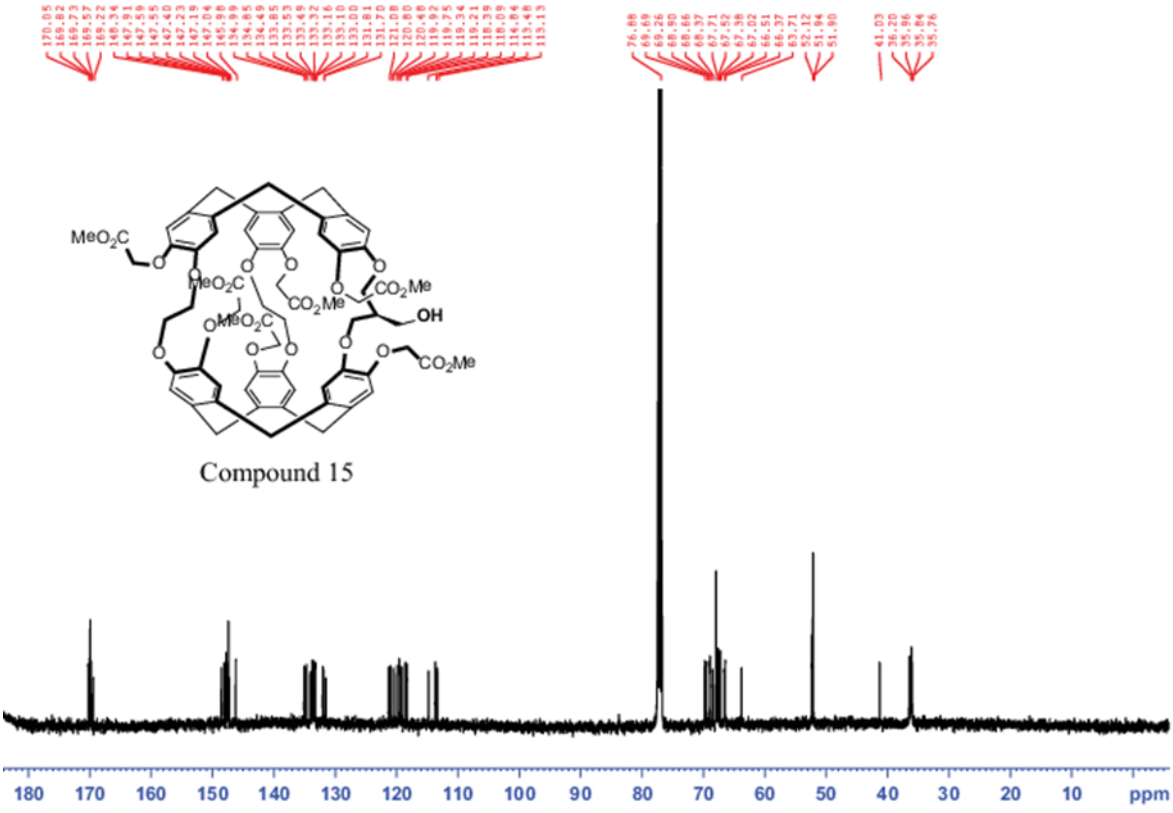

Figure S19: ^{13}C NMR (100.6 MHz) spectrum of compound **15** recorded in $CDCl_3$ at 298 K.

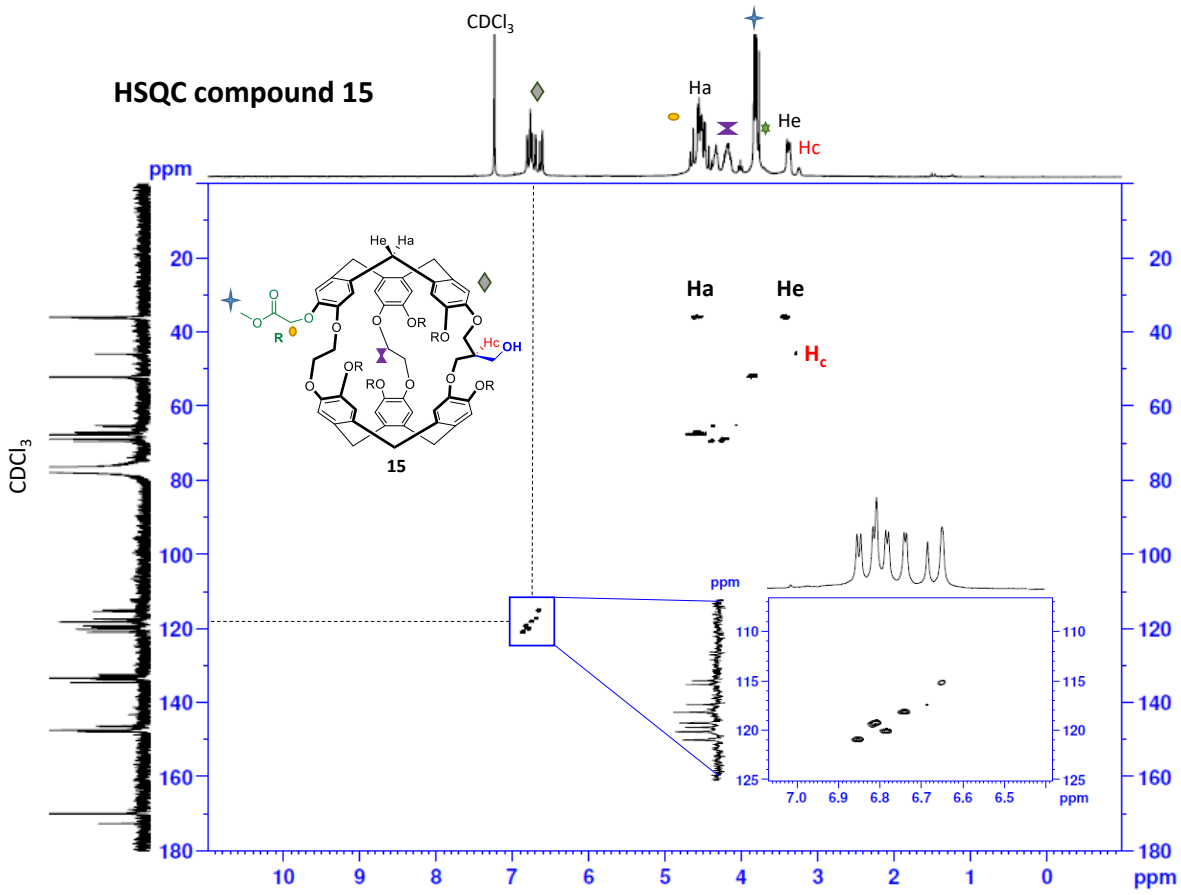

Figure S20: HSQC (400 MHz) spectrum of compound **15** recorded in $CDCl_3$ at 298 K.

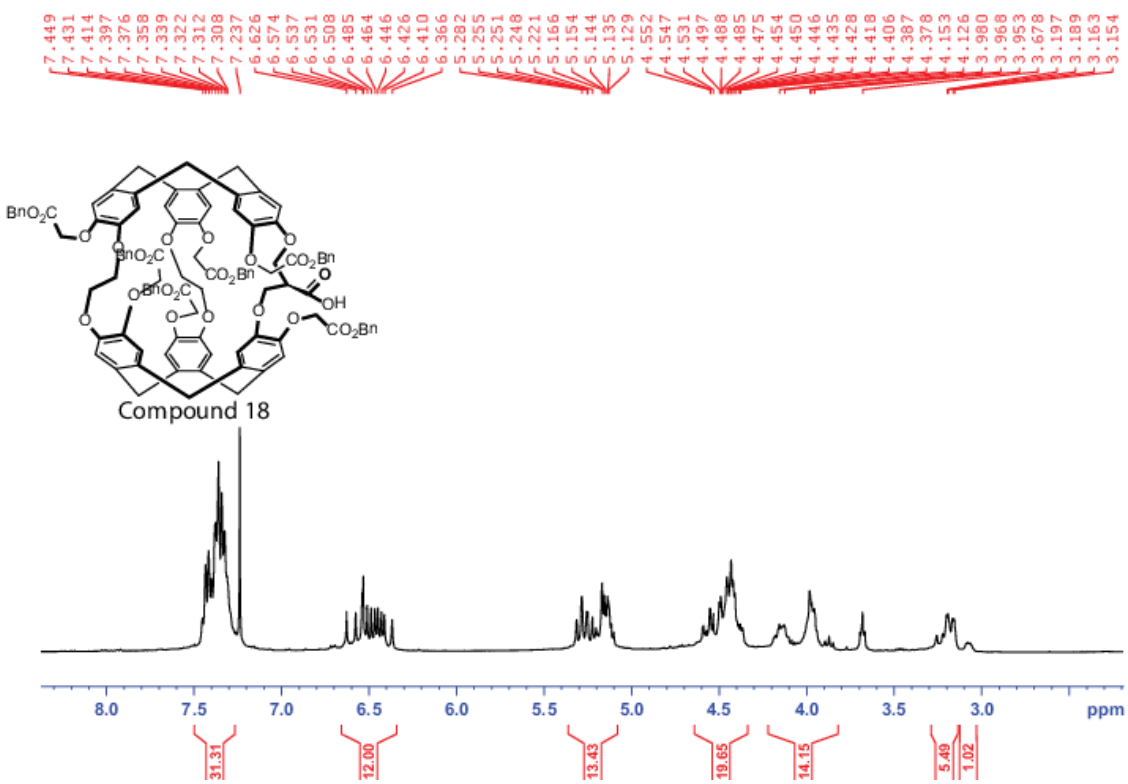

Figure S21: ^{1}H NMR (400 MHz) spectrum of compound **18** recorded in $CDCl_3$ at 298 K.

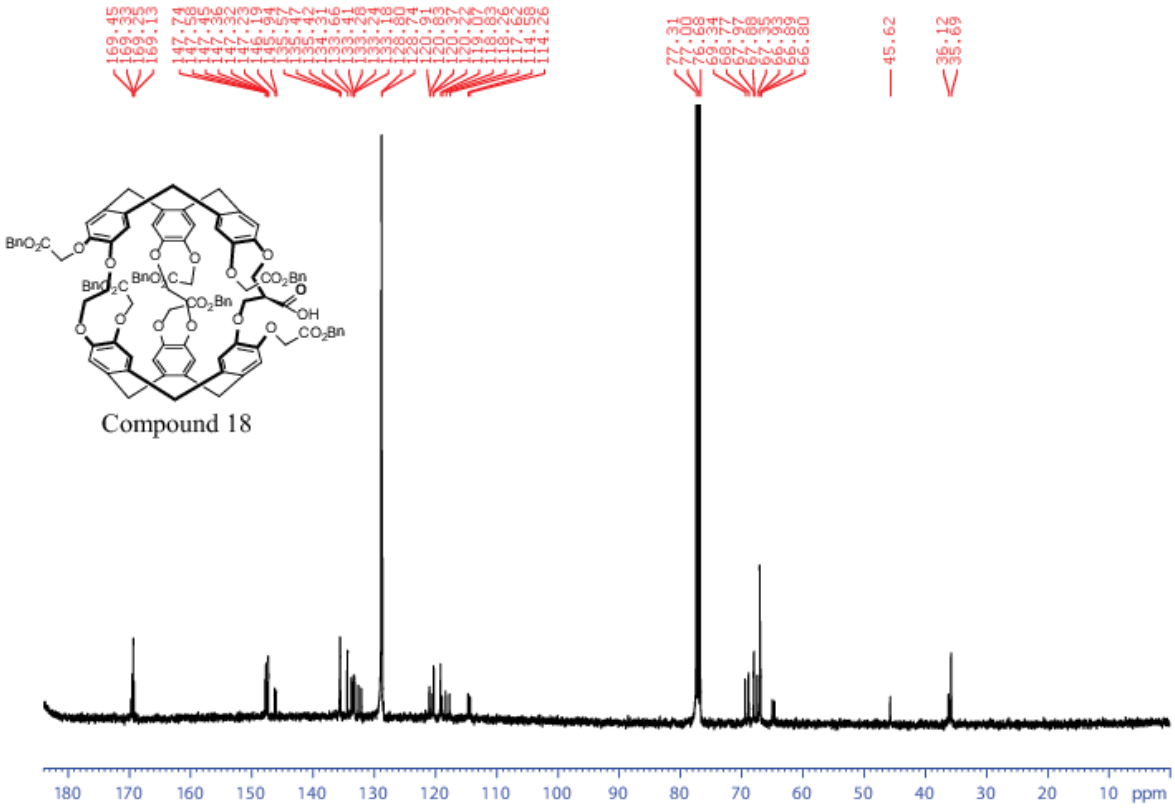

Figure S22: ^{13}C NMR (100.6 MHz) spectrum of compound **18** recorded in $CDCl_3$ at 298 K.

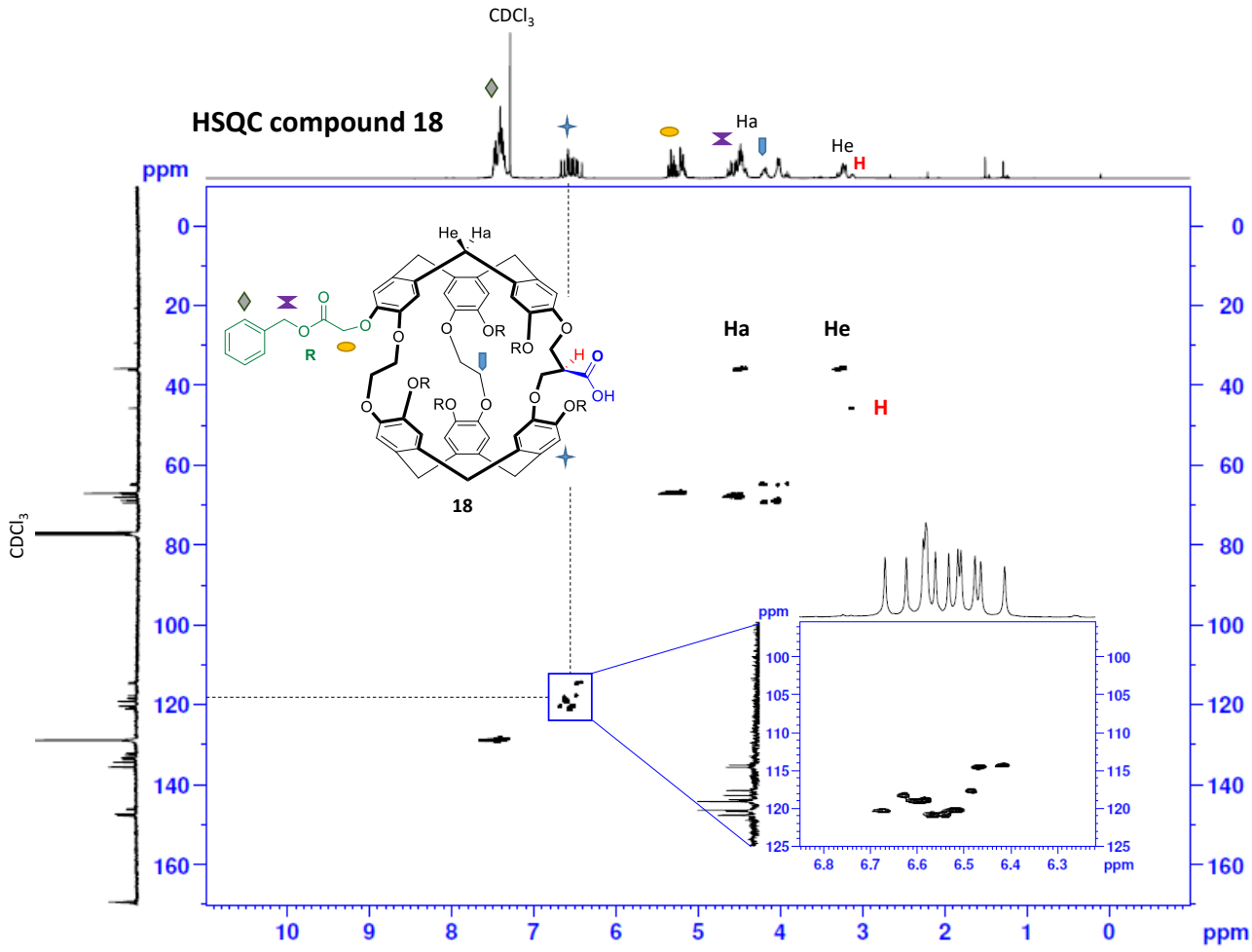

Figure S23: HSQC (400 MHz) spectrum of compound **18** recorded in $CDCl_3$ at 298 K.

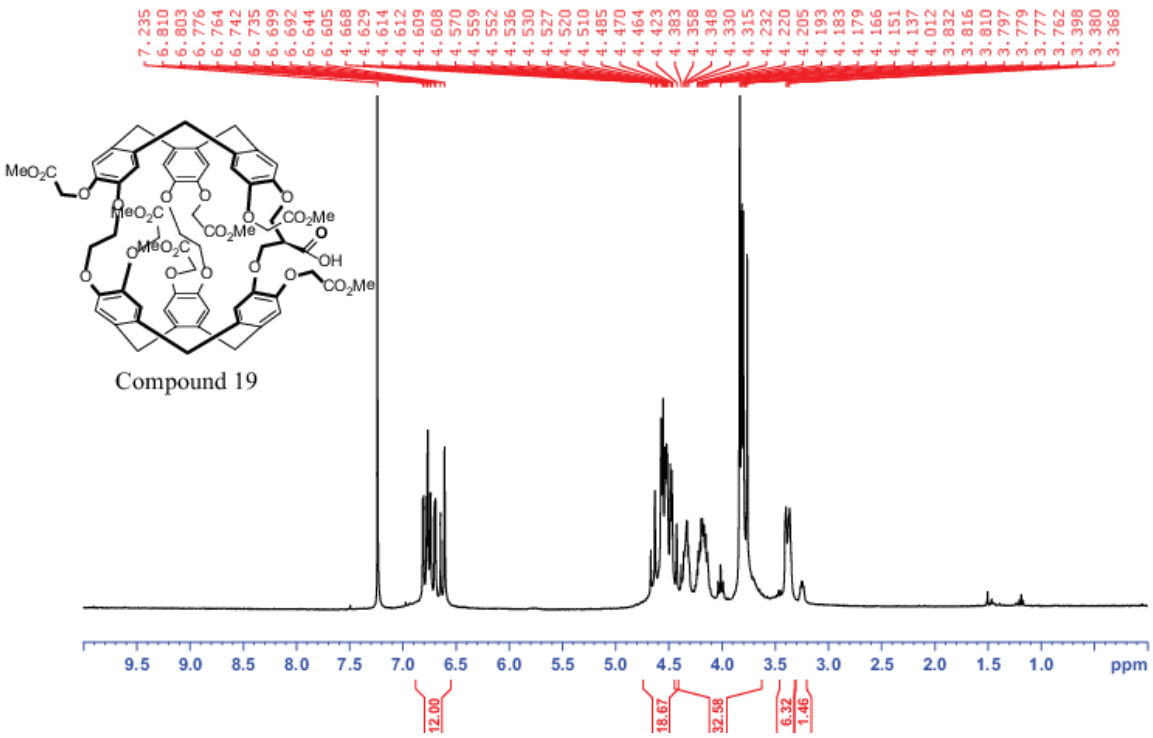

Figure S24: ^{1}H NMR (400 MHz) spectrum of compound **19** recorded in $CDCl_3$ at 298 K.

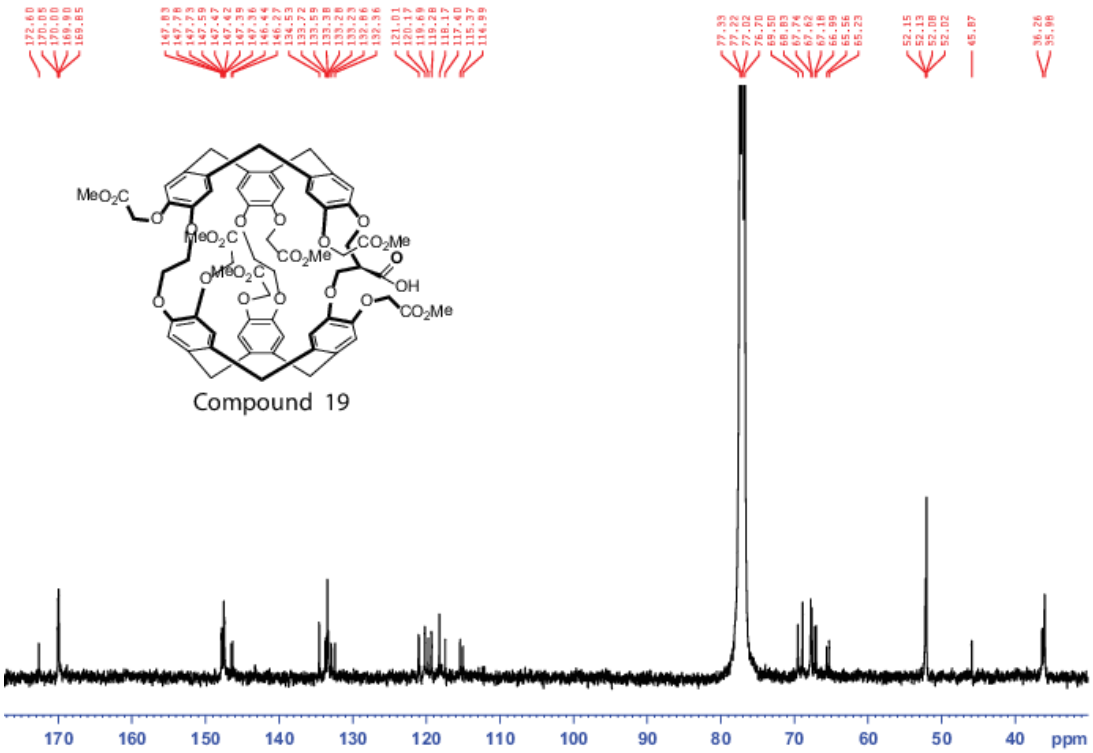

Figure S25: ^{13}C NMR (100.6 MHz) spectrum of compound **19** recorded in $CDCl_3$ at 298 K.

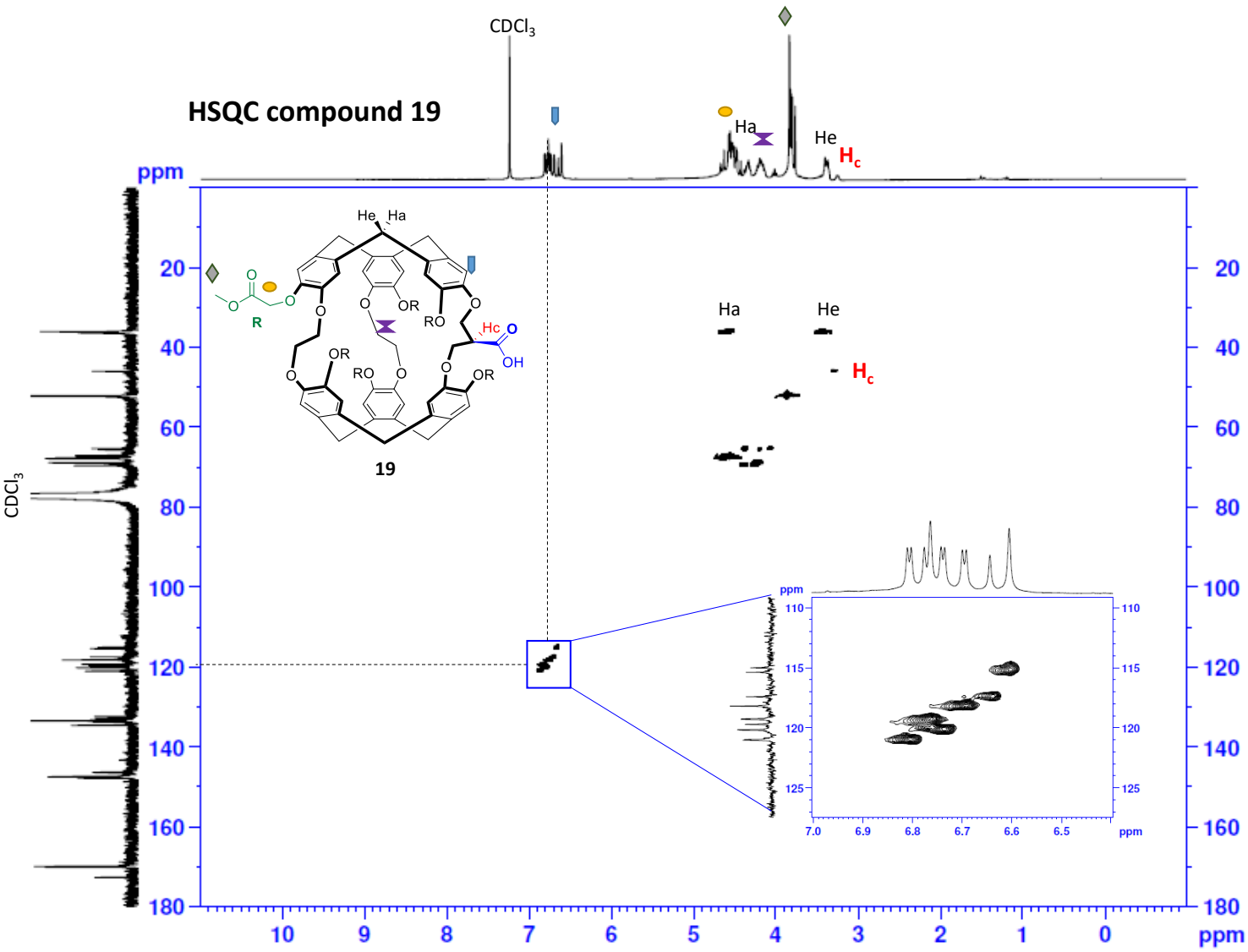

Figure S26: HSQC (400 MHz) spectrum of compound **19** recorded in $CDCl_3$ at 298 K.

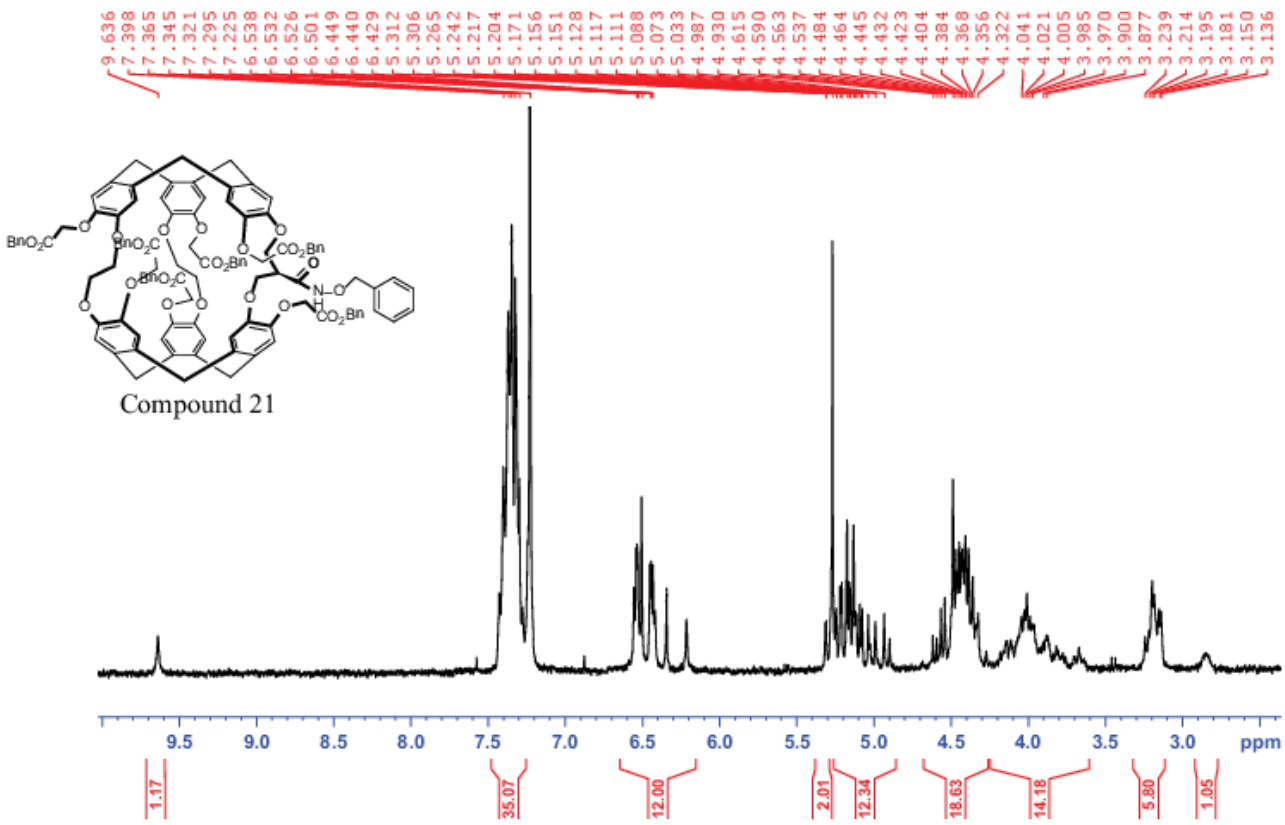

Figure S27: ^{1}H NMR (400 MHz) spectrum of compound **21** recorded in $CDCl_3$ at 298 K.

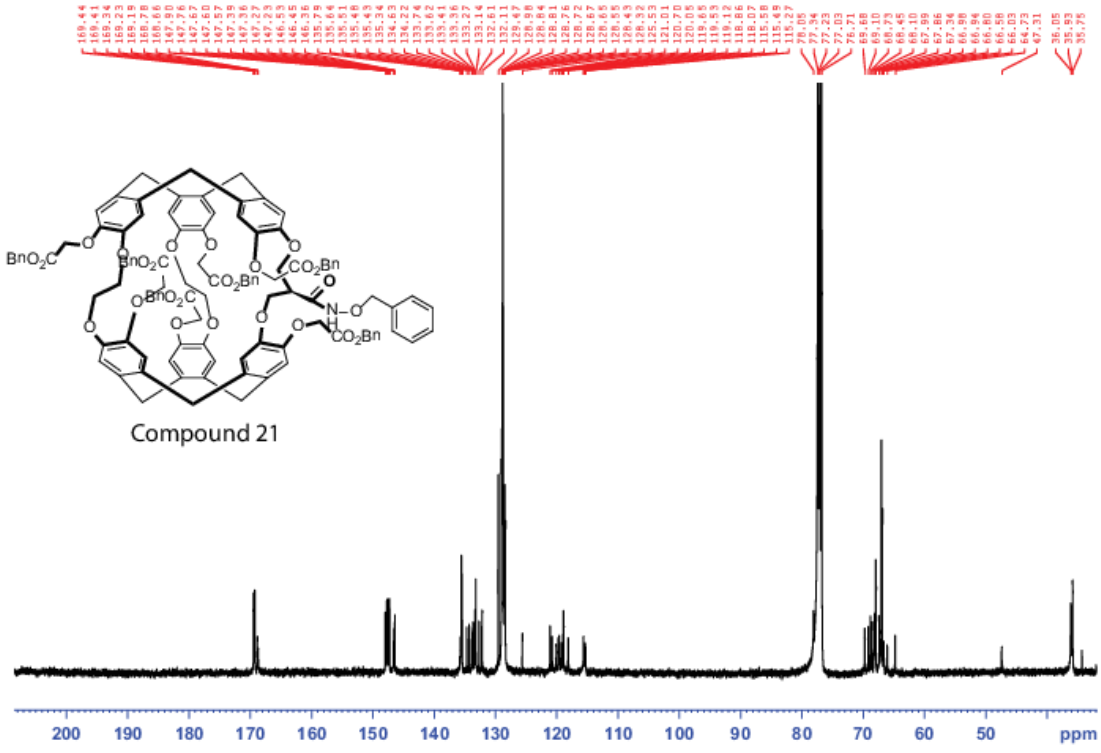

Figure S28: ^{13}C NMR (400 MHz) spectrum of compound **21** recorded in $CDCl_3$ at 298 K.

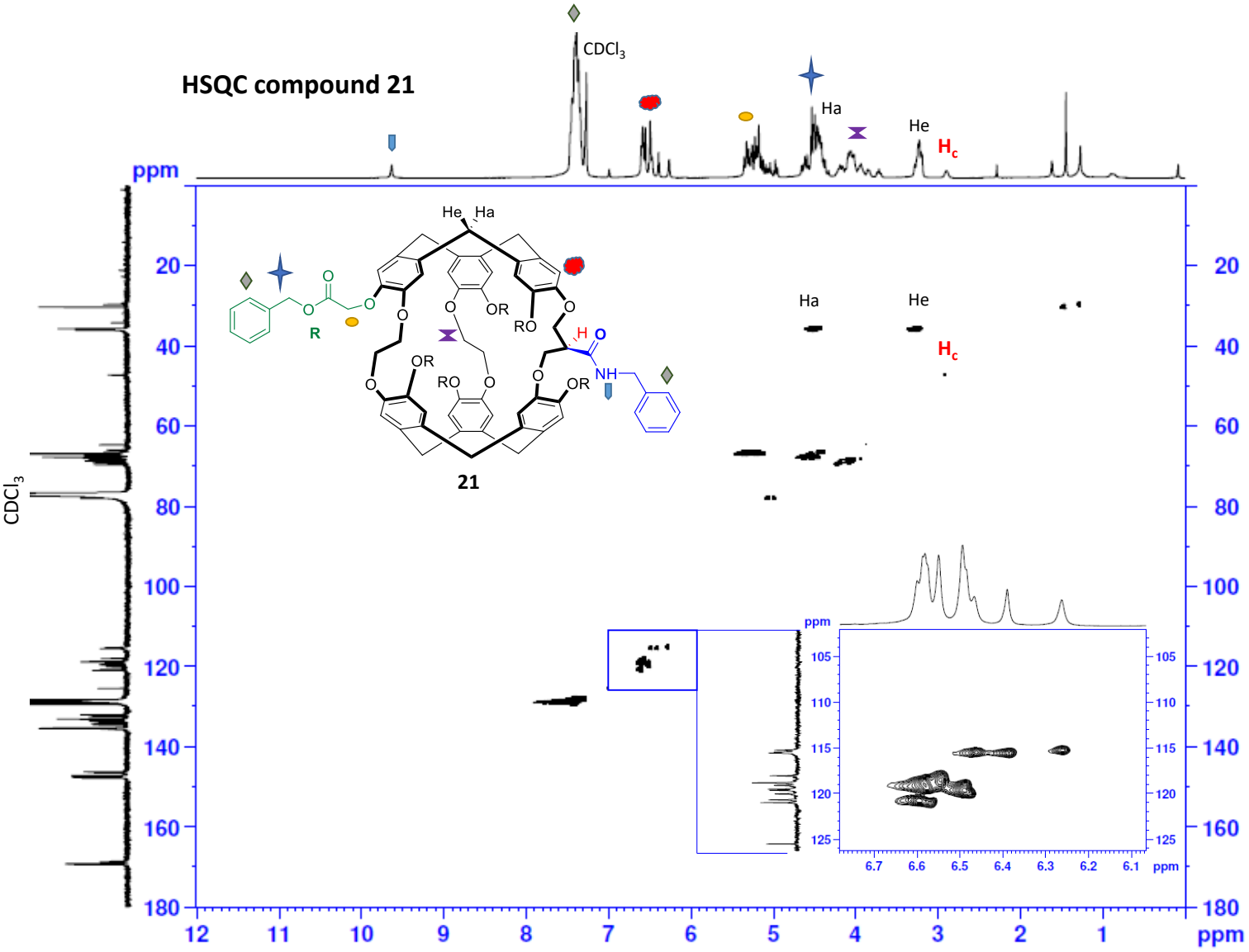

Figure S29: HSQC (400 MHz) spectrum of compound **21** recorded in $CDCl_3$ at 298 K.

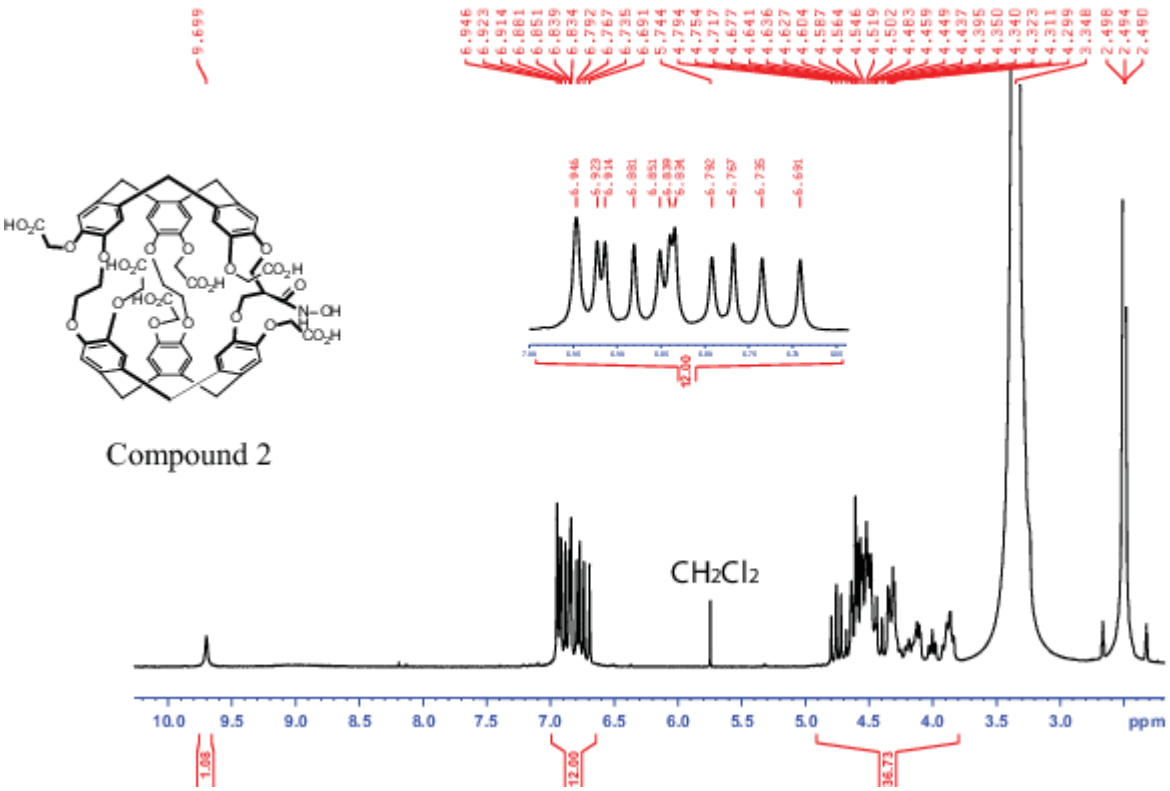

Figure S30: ^{1}H NMR (400 MHz) spectrum of compound **2** recorded in DMSO-d_6 at 298 K.

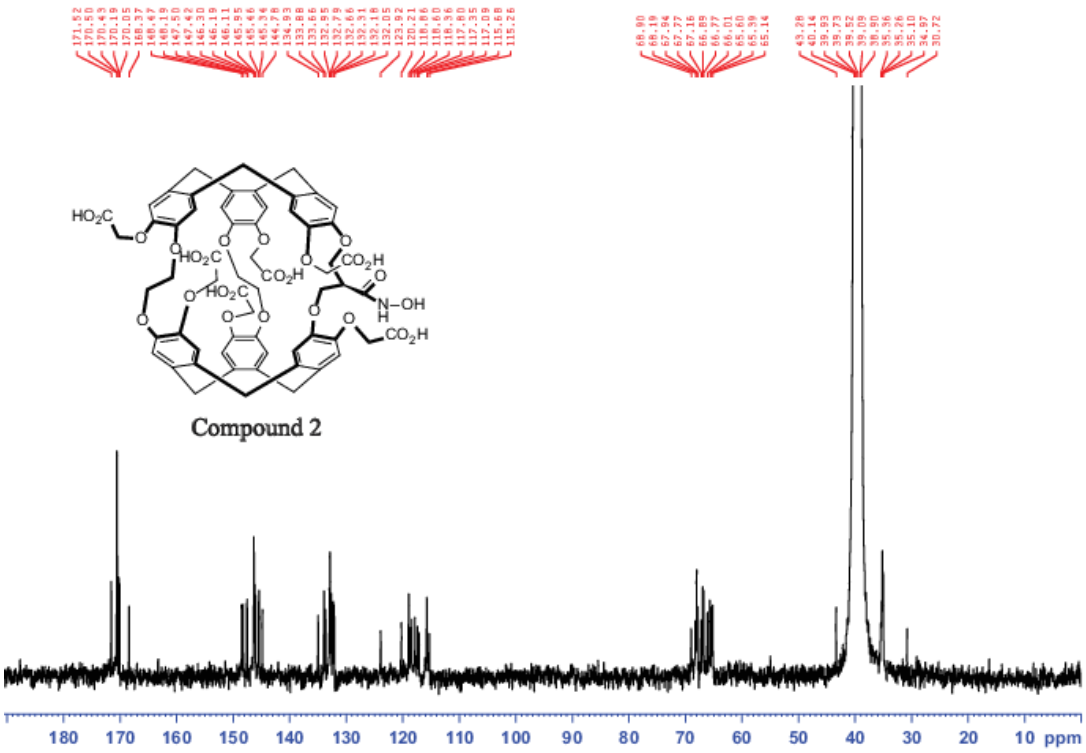

Figure S31: ^{13}C NMR (100.6 MHz) spectrum of compound **2** recorded in DMSO-d_6 at 298 K.

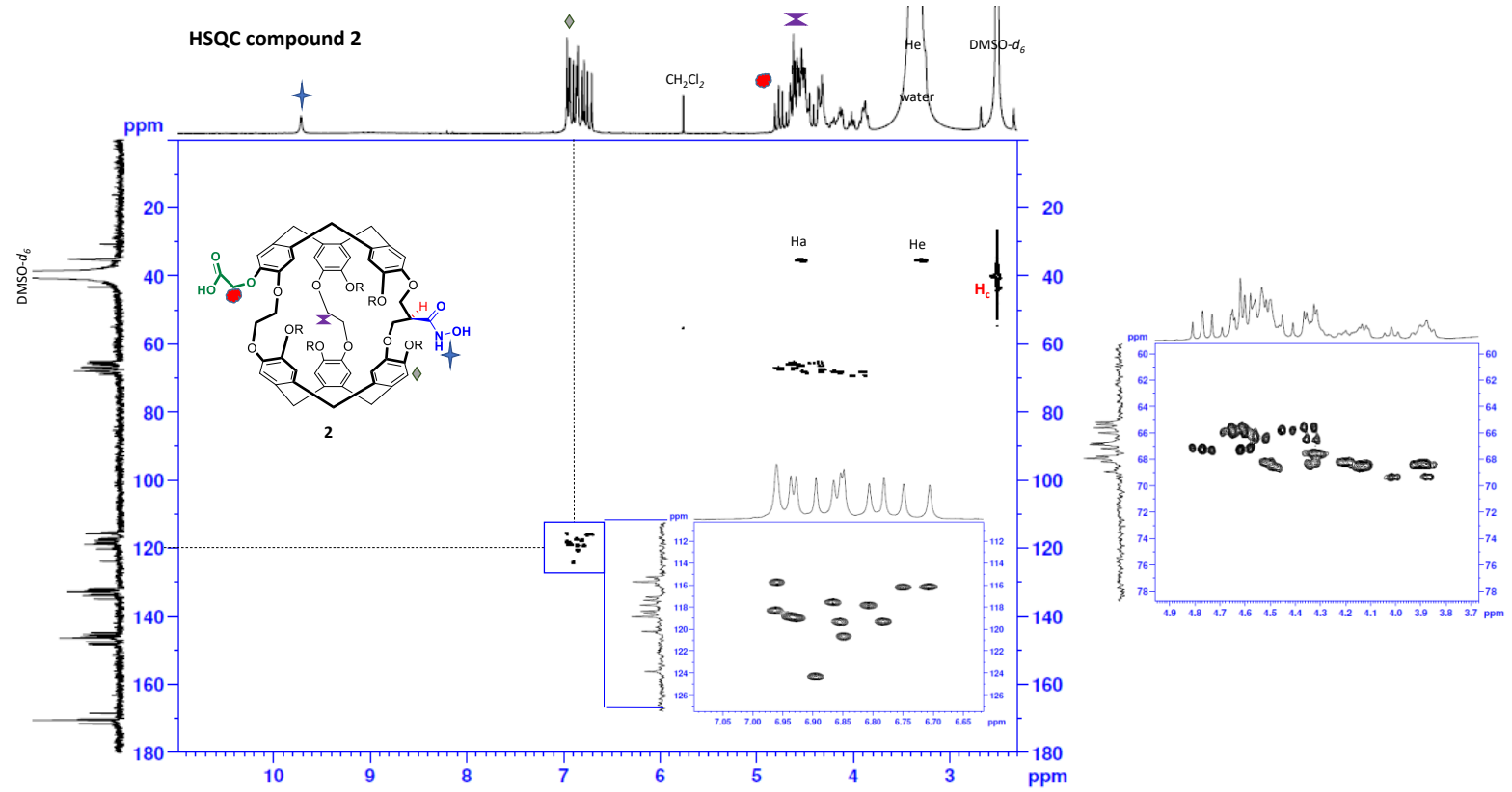

Figure S32: HSQC (400 MHz) spectrum of compound **2** recorded in DMSO-d_6 at 298 K.

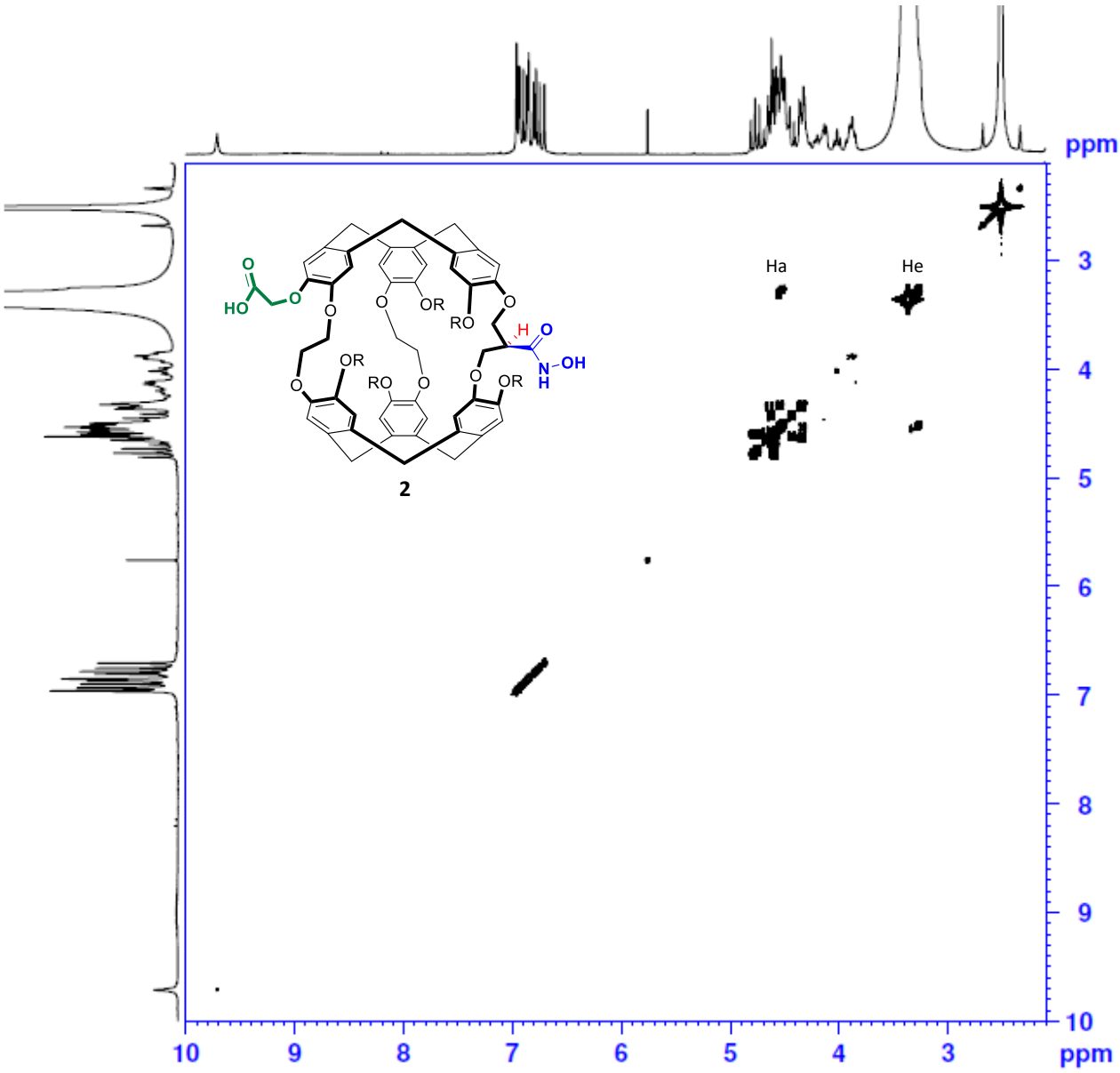

Figure S33: COSY (400 MHz) spectrum of compound **2** recorded in DMSO-d_6 at 298 K.

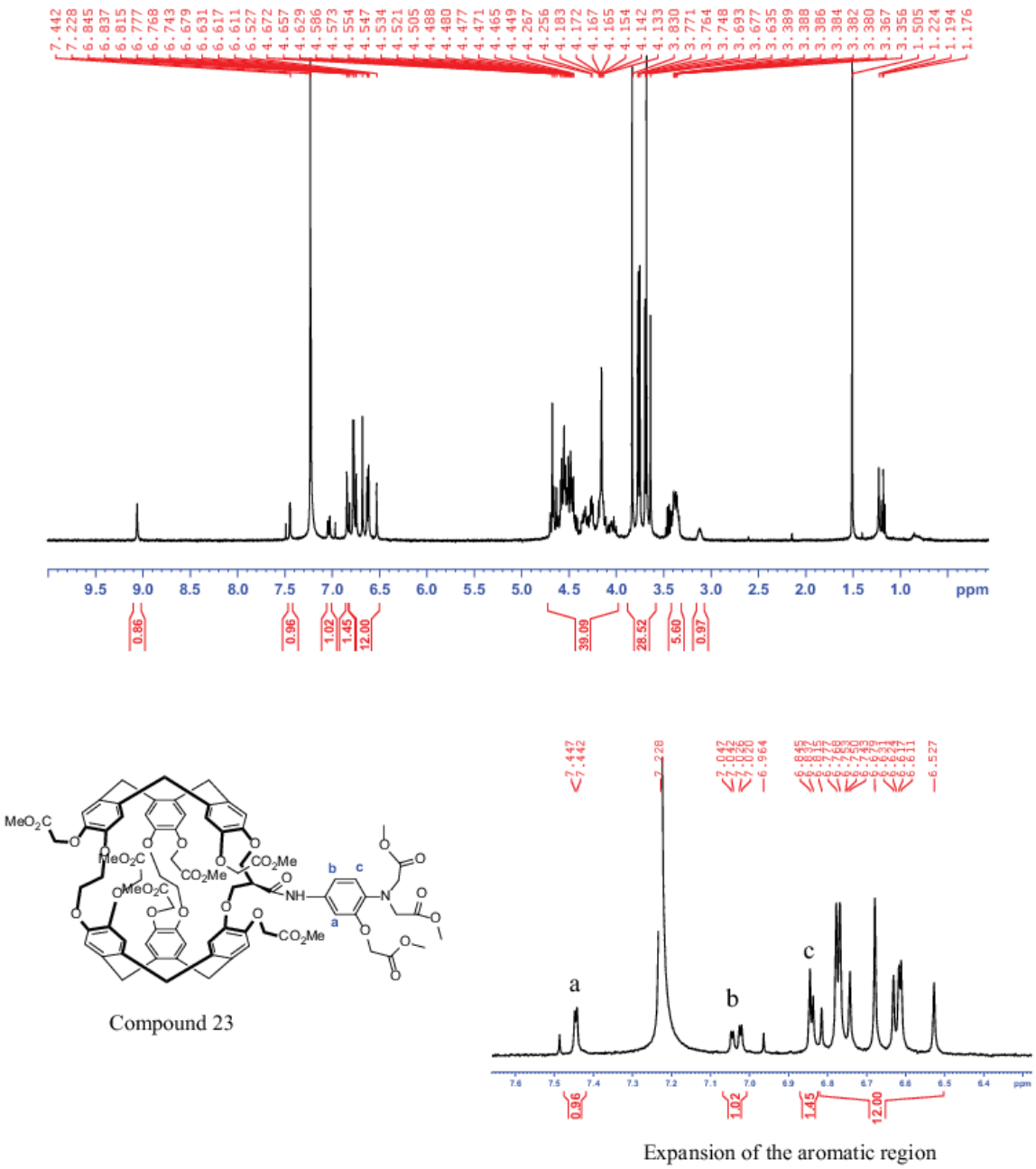

Figure S34: ^{1}H NMR (400 MHz) spectrum of compound **23** recorded in $CDCl_3$ at 298 K.

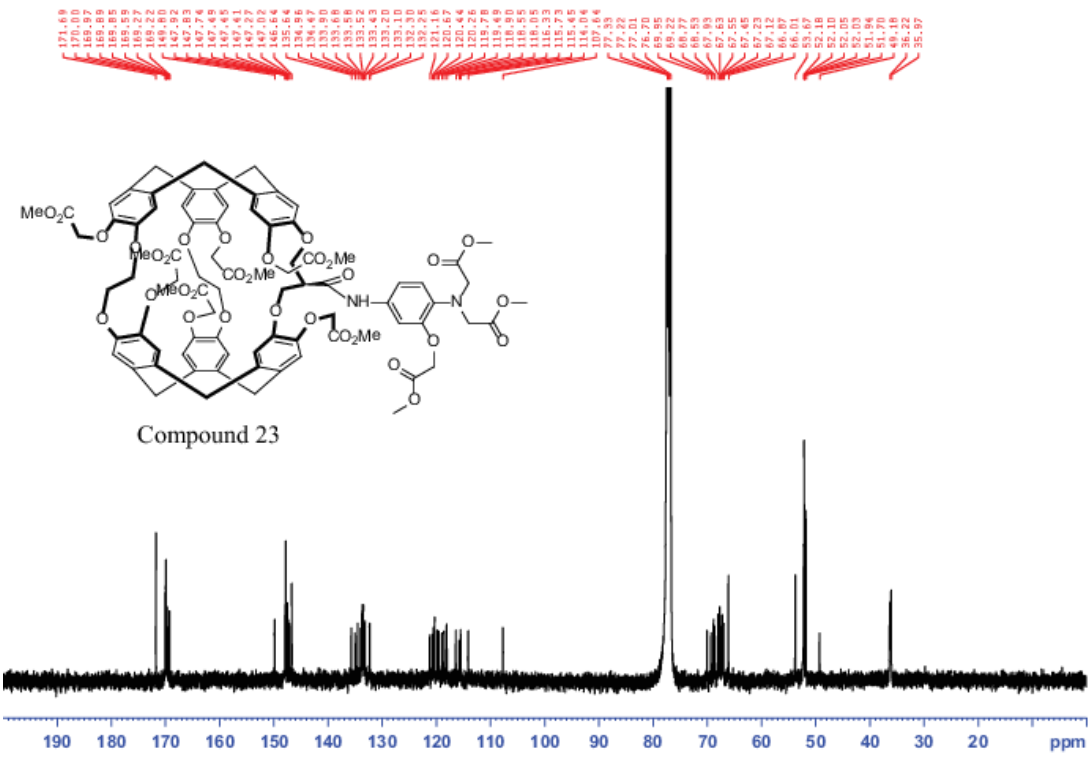

Figure S35: ^{13}C NMR (100.6 MHz) spectrum of compound **23** recorded in $CDCl_3$ at 298 K.

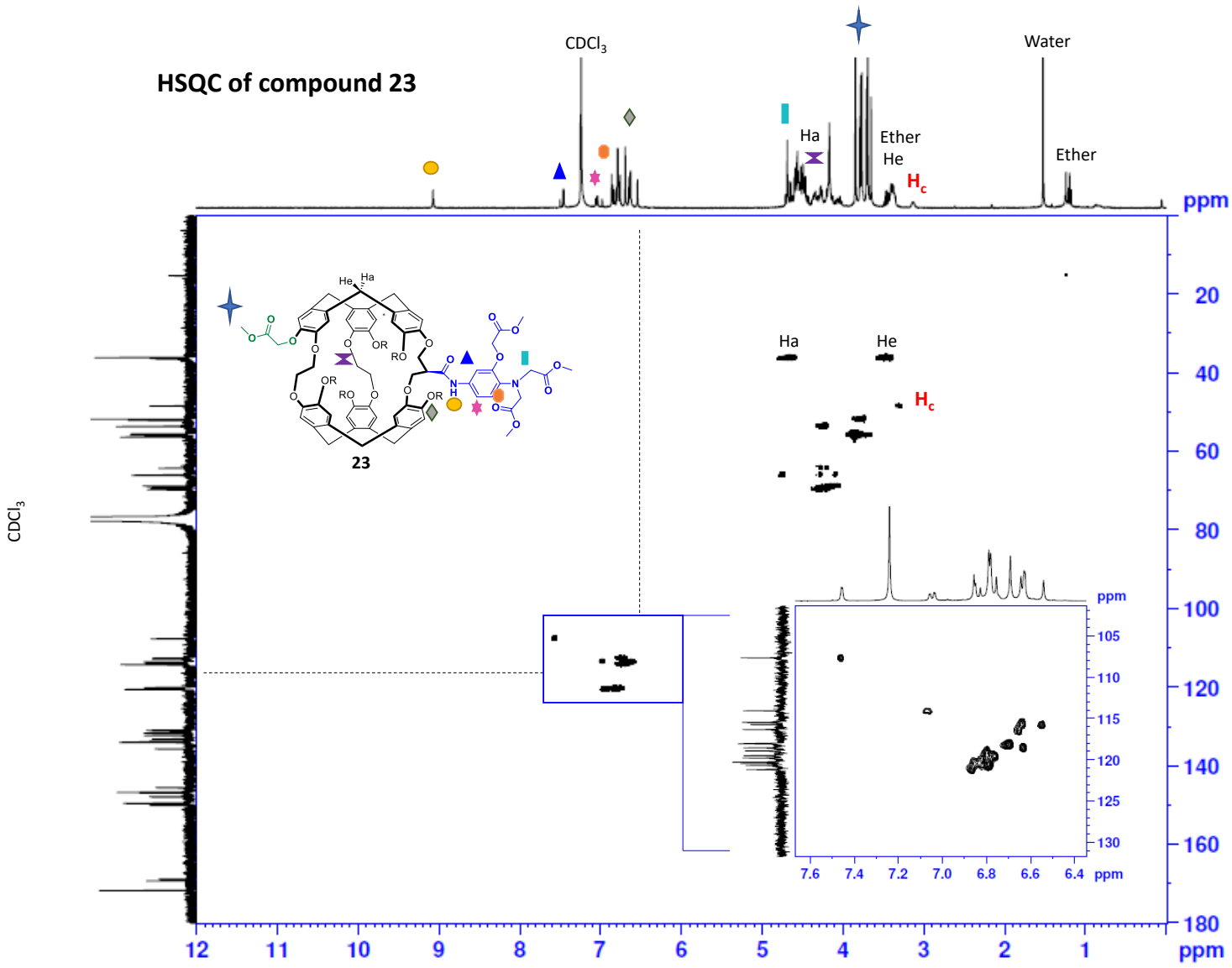

Figure S36: HSQC (400 MHz) spectrum of compound **23** recorded in $CDCl_3$ at 298 K.

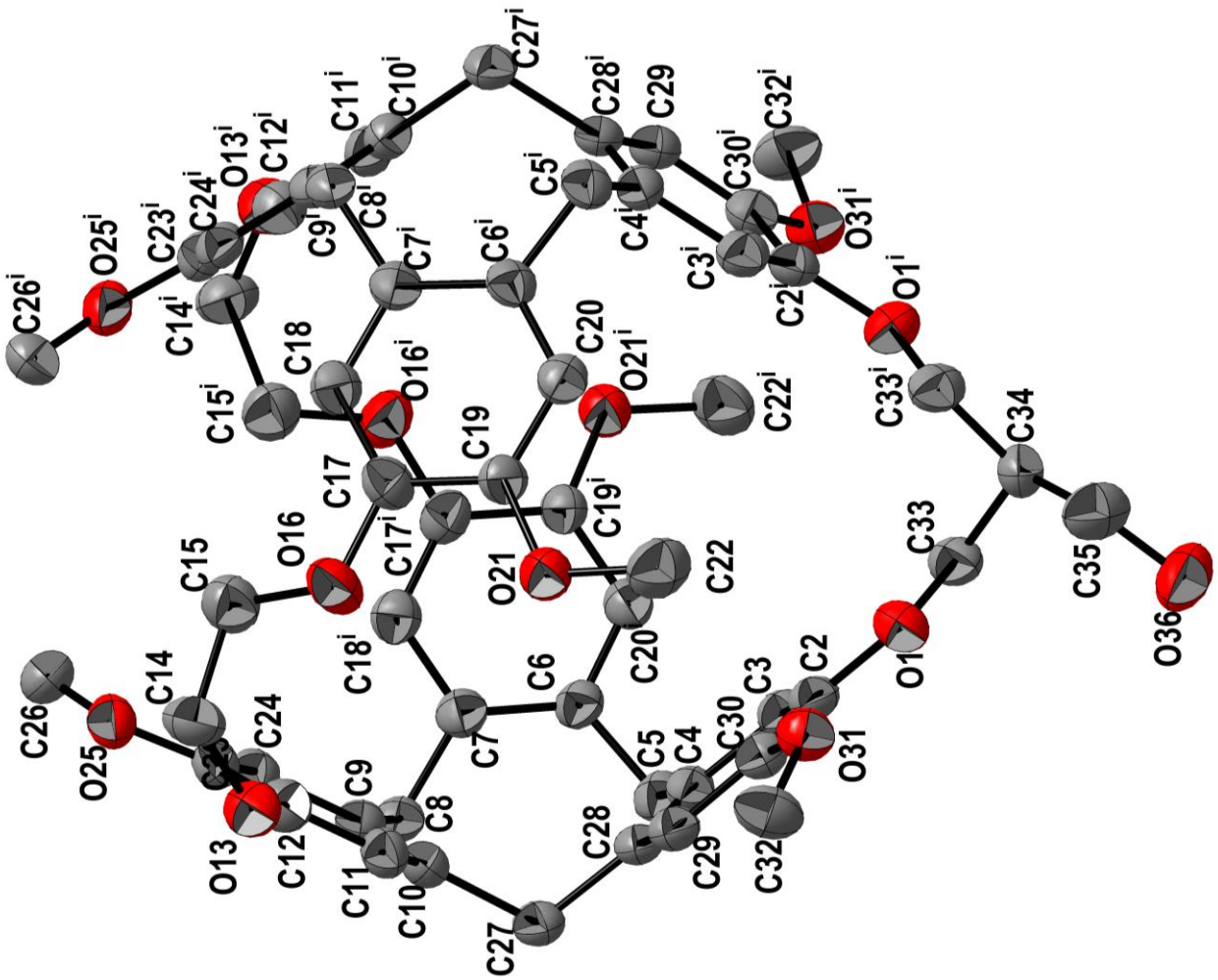

Figure S37: ORTEP representation of compound **9** (hydrogen atoms and solvent molecule were omitted for clarity. The displacement ellipsoids were plotted at 30% probability level).

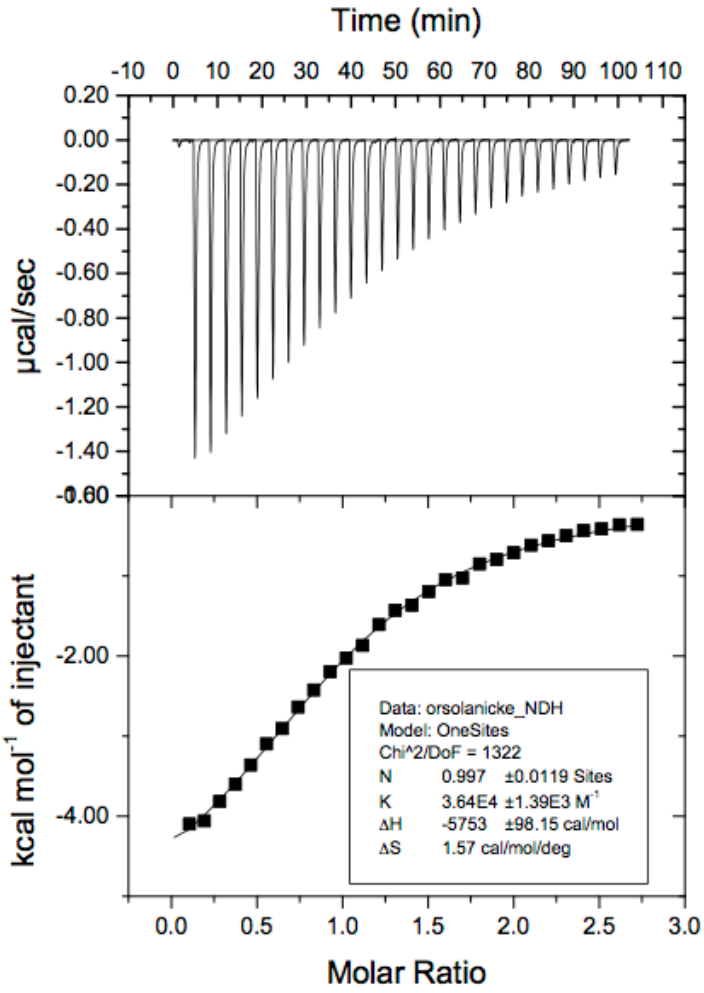

Figure S38: Calorimetric titration of compound **2** in H_2O/TRIS (20 mM; pH = 7.6). The solution host (c = 0.08 mM) was placed into the calorimeter cell (1.4 mL) and 28 successive aliquots (10 µL) of Ni^{2+} solution (c = 1.0 mM) were added at 3 min intervals.

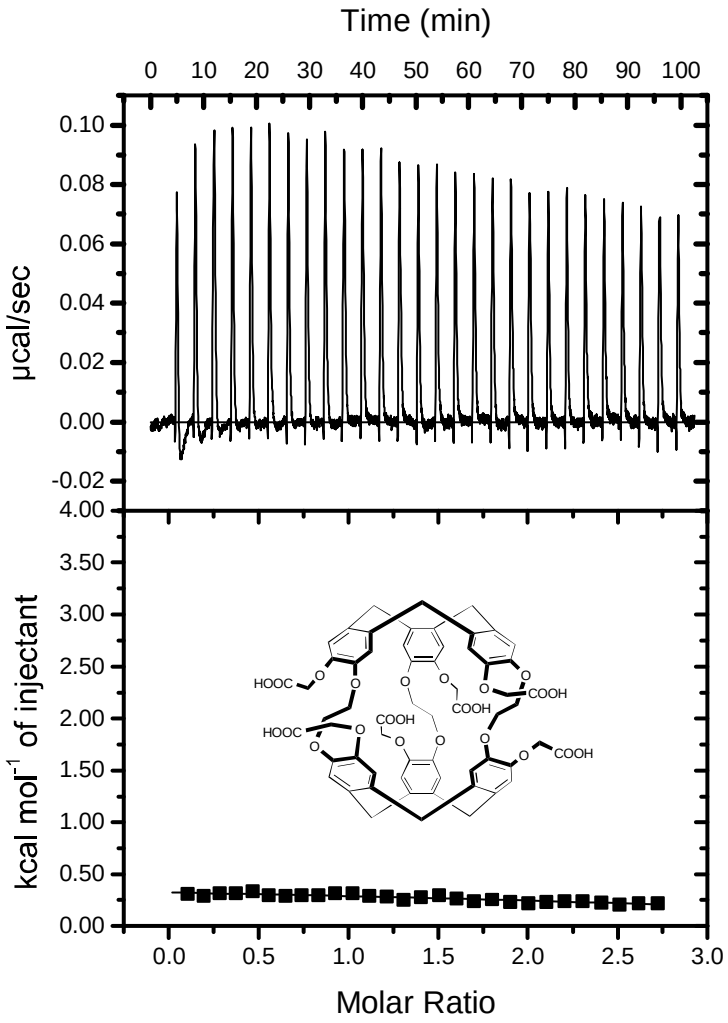

Figure S39: Calorimetric titration of Cryptophane-222 hexacarboxylate in H_2O/TRIS (20 mM; pH = 7.0). The solution host (c = 0.08 mM) was placed into the calorimeter cell (1.4 mL) and 28 successive aliquots (10 µL) of Zn^{2+} solution (c = 1.0 mM) were added at 3 min intervals.

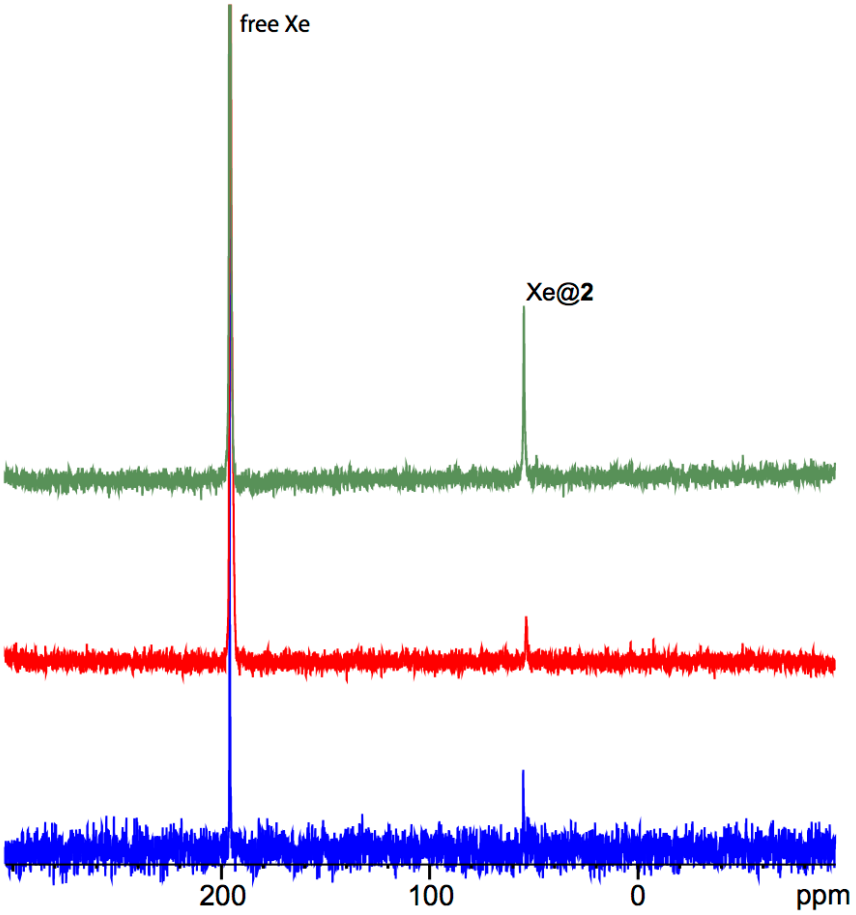

Figure S40: Hyperpolarized 129-xenon spectra (1 scann) of compound **2** in TRIS buffer (20 mM, pH = 7.5). a) in absence of Zn^{2+} (green spectrum). b) in presence of 1.0 equiv. of Zn^{2+} (blue spectrum). c) in presence of 5.0 equiv. of Zn^{2+} (red spectrum). Spectra recorded at 25°C. 0.39 mg of **1** in 1000 µL of TRIS buffer (20 mM)/10% D_2O pH 7.5 (c = 0.32 mM).

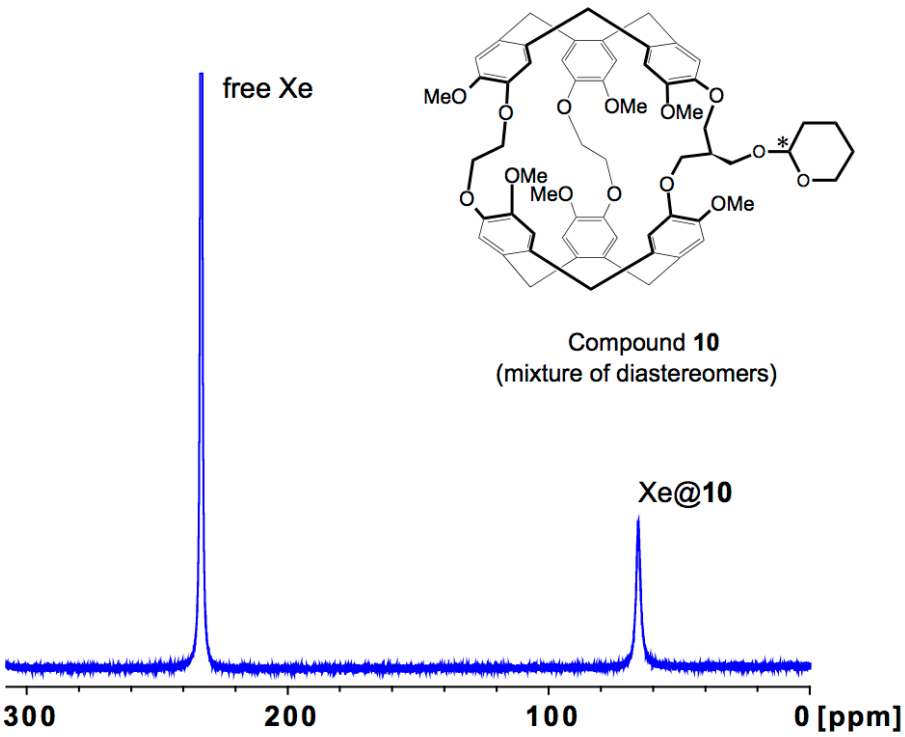

Figure S41: hyperpolarized ^{129}Xe NMR spectrum of compound **10** recorded at 298 K in $C_2D_2Cl_4$. 1.8 mg of cryptophane **10** in 600 µL of 1,1,2,2-tetrachloroethane-d_2.

Crystal data

$C_{56}H_{58}O_{13}$	D_x = 0.987 Mg m^{-3}
M_r = 939.07	Cu *K*a radiation, l = 1.54184 Å
Cubic, $I2_13$	Cell parameters from 3819 reflections
Hall symbol: I 2b 2c 3	q = 3.2–66.9°
a = 33.5971 (16) Å	m = 0.57 mm^{-1}
V = 37923 (5) Å^3	*T* = 150 K
Z = 24	Plate, colorless
F(000) = 11952	0.40 × 0.32 × 0.19 mm

Data collection

Xcalibur, Atlas, Gemini ultra diffractometer	10442 independent reflections
Radiation source: fine-focus sealed X-ray tube, Enhance Ultra (Cu) X-ray Source	6339 reflections with *I* > 2.0s(*I*)
Mirror monochromator	R_{int} = 0.069
Detector resolution: 10.4685 pixels mm^{-1}	q_{max} = 67.0°, q_{min} = 3.2°
w scans	*h* = -38®28
Absorption correction: analytical *CrysAlis PRO* 1.171.38.46 (Rigaku Oxford Diffraction, 2015) Analytical numeric absorption correction using a multifaceted crystal model based on expressions derived by R.C. Clark & J.S. Reid. (Clark, R. C. & Reid, J. S. (1995). Acta Cryst. A51, 887-897) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.	*k* = -40®10
T_{min} = 0.863, T_{max} = 0.912	*l* = -29®26
25070 measured reflections	

Refinement

Refinement on F^2	Hydrogen site location: difference Fourier map
Least-squares matrix: full	H-atom parameters constrained
$R[F^2 > 2s(F^2)]$ = 0.078	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯+ A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 347. 529. 246. 53.0
$wR(F^2)$ = 0.189	$(D/s)_{max}$ = 0.003
S = 1.00	$D\rho_{max}$ = 0.53 e Å^{-3}
645 parameters	Absolute structure: Parsons, Flack & Wagner (2013), 3517 Friedel Pairs
60 restraints	Absolute structure parameter: 0.473 (13)
Primary atom site location: other	

Table S1: Crystallographic data of cryptophane **9**.