Supplementary information for

Access to the *Syn* Diastereomers of Cryptophane Cages using HFIP.

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1. Materials and instrumentation

Starting material and solvents were of commercial grade and were used without further purification. Column chromatography was carried out with Merck 60 A (0.040−0.063 mm) silica gel. TLC was performed with Merck silica gel 60 F254 plates. ^{1}H NMR and ^{13}C NMR were recorded at 298 K on a Bruker Advance III HD 300 MHz spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts (δ) are reported in ppm and referenced to the protonated residual solvent signal.

2. Synthetic procedures

Synthesis of 1

In a dry two-necked round-bottom flask was added P_2O_5 (30 g, 0.11 mol, 1.5 equiv.) and dry Et_2O (85 mL). The mixture was heated to 48°C and a solution of 3-methoxybenzyl alcohol (10 g, 0.07 mol, 1 equiv.) in 105 mL of Et_2O was added dropwise with an extra funnel over 2h. Stirring was stopped and the reaction was performed overnight under reflux. Et_2O was decanted, and the solid was washed and sonicated with dichloromethane (3 x 40 ml). The organic layers were combined and evaporated under reduced pressure. The resulting oil was purified by silica gel column chromatography using CH_2Cl_2/Hexane (2/3) as eluent. A yellow solid was obtained, was dissolved in a minimum amount of dichloromethane and precipitated with a mixture of pentane/Et_2O (7/3). A white solid was collected by filtration to give compound **1**. (1 g, 11%).
Characterizations of **1** was consistent with literature.[1]

^{1}H NMR ($CDCl_3$, 400 MHz, 298K) δ 7.27 (d, J = 8.38 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.66 (dd, ^{3}J= 8.5 Hz, ^{4}J = 2.8 Hz, 1H), 4.76 (d, J = 13.6 Hz, 1H), 3.74 (s, 3H), 3.64 (d, J = 13.6 Hz, 1H).

Synthesis of 2

A solution of boron tribromide (70 mL, 1 M in dichloromethane, 15.5 equiv.) was added dropwise to a suspension of compound **1** (1.65 g, 4.5 mmol, 1 equiv.) in dry dichloromethane (25 mL) at 0°C. The solution was warmed to room temperature and stirred overnight. The mixture was poured into an ice and H_2O slurry. The solid residue was washed with 100 mL of hot water and dried to provide a slightly colored powder. The powder was poured into 7 mL of acetonitrile and sonicated for 20 min. The precipitate was filtered, washed with 10 mL of Et_2O and dried to give compound **2** (500 mg, 56%).
Characterizations of **2** was consistent with literature.[2]

^{1}H NMR (400 MHz, acetone-d_6, 298K) δ 7.21 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 2.6 Hz, 1H), 6.55 (dd, ^{3}J = 8.3 Hz, ^{4}J = 2.6 Hz, 1H), 4.78 (d, J = 13.4 Hz, 1H), 3.55 (d, J = 13.4 Hz, 1H).

Synthesis of 4

To **2** (30 mg, 94.2 μmol, 1 equiv.) dissolved in DMF (2.5 mL), were added **3** (111 mg, 320 μmol, 3.4 equiv.) and Cs_2CO_3 (138 g, 424 μmol, 4.5 equiv.). The reaction mixture was stirred at 80 °C for 18 hours. It was diluted with distilled water (5 mL), extracted with $CHCl_3$ (2 x 10 mL) and dried over $MgSO_4$. Organic solvents were removed under reduced pressure. The resulting solid was washed with diethyl ether and purified by silica gel column chromatography using $CHCl_3$/CH_3OH (95/5) as eluent to give **4** as a white solid (78 mg, 74%).
Characterization of **4** was consistent with literature.[3]

^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 7.26 (d, *J* = 8.4 Hz, 3H), 6.93 (d, *J* = 2.7 Hz, 3H), 6.92-6.89 (m, 9H), 6.67 (dd, ^3J = 8.3 Hz, ^4J = 2.6 Hz, 3H), 4.75 (d, *J* = 13.2 Hz, 3H), 4.72 (d, *J* = 11.8 Hz, 3H), 4.68 (m, 3H), 4.45 (d, *J* = 11.8 Hz, 3H), 4.33-4.25 (m, 12H), 3.95-3.88 (m, 3H), 3.85 (s, 9H), 3.63 (d, *J* = 11.8 Hz, 3H), 3.57-3.52 (m, 3H), 1.90-1.82 (m, 3H), 1.77-1.70 (m, 3H), 1.67-1.55 (m, 12H).

TLC: Rf ($CHCl_3$/CH_3OH : 95/5) = 0.50.

Synthesis of *anti*-5 (Cryptophane C) and *syn*-5 (Cryptophane D)

4 (50 mg, 45 μmol, 1 equiv.) was dissolved into 50 mL of a mixture of chloroform/HFIP (1/1). After complete dissolution of **4**, $KHSO_4$ (4 mg, 29 μmol, 0.7 equiv.) was added. The reaction mixture was stirred for 20 hours. The solvents were evaporated and resulting oil was dissolved in 15 mL of dichloromethane, washed with water (20 mL) and extracted with dichloromethane (2 x 15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated and the resulting solid was purified by silica gel column chromatography using CH_2Cl_2/CH_3COCH_3 (95/5) as eluent to yield ***anti*-5** (10 mg, 31%) and ***syn*-5** (6 mg, 18%) as white solids.
Characterizations of ***anti*-5** and ***syn*-5** were consistent with literature.[3,4]

***anti*-5** - ^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 7.09 (d, *J* = 8.5 Hz, 3H), 6.79 (d, *J* = 2.6 Hz, 3H), 6.67 (s, 3H), 6.62 (s, 3H), 6.36 (dd, ^3J = 8.4 Hz, ^4J = 2.7 Hz, 3H), 4.61 (d, *J* = 13.7 Hz, 3H), 4.60 (d, *J* = 13.5 Hz, 3H), 4.38-4.29 (m, 6H), 4.25-4.26 (m, 3H), 4.07-4.02 (m, 3H), 3.80 (s, 9H), 3.51 (d, *J* = 13.6 Hz, 3H), 3.39 (d, *J* = 13.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, 298K) δ 156.6, 148.6, 147.4, 141.19, 132.9, 132.3, 131.9, 131.0, 119.6, 116.7, 114.8, 111.8, 66.9, 65.5, 56.6, 36.4, 36.2.

TLC: Rf CH_2Cl_2/CH_3COCH_3 (95/5) = 0.35

***syn*-5** - ^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 7.10 (d, *J* = 8.5 Hz, 3H), 6.83 (s, 3H), 6.66 (s, 3H), 6.68-6.65 (m, 6H), 4.62 (d, *J* = 13.8 Hz, 3H), 4.60 (d, *J* = 13.6 Hz, 3H), 4.32-4.23 (m, 6H), 4.16-4.01 (m, 3H), 3.81 (s, 9H), 3.70-3.64 (m, 3H), 3.50 (d, *J* = 13.6 Hz, 3H), 3.45 (d, *J* = 13.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, 298K) δ 157.3, 150.1, 147.0, 141.0, 134.9, 132.4, 132.0, 131.0, 131.3, 119.1, 114.2, 113.5, 71.6, 66.2, 56.3, 36.4, 36.2.

TLC: Rf CH_2Cl_2/CH_3COCH_3 (95/5) = 0.56

Synthesis of 6a

Vanillic alcohol (45.0 g, 292 mmol, 1 equiv.) was dissolved in absolute alcohol (500 mL). K_2CO_3 (45.0 g, 331 mmol, 1.13 equiv.) and dibromoethane (100 mL, 1.16 mol, 3.97 equiv.) were added under stirring. The mixture was stirred at 78°C for 6 hours. The solvent was removed under reduced pressure, then water (300 mL) and ethyl acetate (200 mL) were added to the residue. The solution was stirred at room temperature overnight, filtered and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with 10% aqueous NaOH (4 x 100 mL), brine (100 mL) and dried over $MgSO_4$. Organic solvent was removed and the crude product was dissolved in warmed diisopropyl ether (300 mL). The solution was cooled and the brown oil was eliminated by decantation. Evaporation of the solvent afforded **6a** as a white solid (36.0 g, 47%).
Characterization of **6a** was consistent with literature.[5]

^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 6.95 (s, 1H), 6.94-6.85 (m, 2H), 4.62 (s, 2H), 4.32 (t, *J* = 6.7 Hz, 2H), 3.87 (s, 3H), 3.64 (t, *J* = 6.7 Hz, 2H), 1.79 (s, 1H).

Synthesis of 6b

Vanillic alcohol (5.0 g, 33 mmol, 1 equiv.) was dissolved in absolute alcohol (50 mL). K_2CO_3 (5.0 g, 37 mmol, 1.13 equiv.) and dibromopropane (13 mL, 129 mmol, 3.97 equiv.) were added under stirring. The mixture was stirred at 78°C for 6 hours. The solvent was removed under reduced pressure, then water (25 mL) and ethyl acetate (35 mL) were added to the residue. The solution was stirred at room temperature overnight, filtered and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with 10% aqueous NaOH (4 x 10 mL), brine (10 mL) and dried over $MgSO_4$. Organic solvent was removed and the crude product was purified by silica gel column chromatography using CH_2Cl_2 as eluent to yield **6b** as a white solid (5.5 g, 60%).
Characterization of **6b** was consistent with literature.[5]

^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 6.94 (s, 1H), 6.88 (s, 2H), 6.62 (d, *J* = 2.6 Hz, 2H), 4.15 (t, *J* = 6.0 Hz, 2H), 3.87 (s, 3H), 3.63 (t, *J* = 6.0 Hz, 2H), 2.36 (q, *J* = 6.1 Hz, 2H), 1.66 (t, *J* = 2.6 Hz, 1H).

TLC: Rf (CH_2Cl_2) = 0.20.

Synthesis of 7a

In a dry round-bottom flask, compound **6a** (12.0 g, 46 mmol, 1 equiv.) was dissolved in anhydrous acetonitrile (200 mL) and scandium triflate (638 mg, 1.30 mmol, 0.03 equiv.) was added. The mixture was stirred at 82 °C for 48 hours. Solvent was evaporated and the resulting mixture was purified by silica gel column chromatography using CH_2Cl_2 as eluent to yield **7a** as a white solid (3.5 g, 31%).
Characterization of **7a** was consistent with literature.[6]

^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 6.92 (s, 3H), 6.84 (s, 3H), 4.75 (d, *J* = 13.7 Hz, 3H), 4.31-4.27 (m, 6H), 3.84 (s, 9H), 3.59-3.55 (m, 9H).

TLC: Rf (CH_2Cl_2) = 0.35.

Synthesis of 7b

In a dry round-bottom flask, compound **6b** (3.8 g, 12 mmol, 1 equiv.) was dissolved in anhydrous acetonitrile (100 mL) and scandium triflate (182 mg, 0.4 mmol, 0.03 equiv.) was added. The mixture was stirred at 82 °C for 48 hours. Solvent was evaporated and the resulting mixture was purified by silica gel column chromatography using CH_2Cl_2 as eluent to yield **7b** as a white solid (1.28 g, 40%).
Characterization of **7b** was consistent with literature.[7]

^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 6.91 (s, 3H), 6.85 (s, 3H), 4.76 (d, *J* = 13.7 Hz, 3H), 4.14-4.11 (m, 6H), 3.83 (s, 9H), 3.63-3.47 (m, 6H), 2.35-2.28 (m, 6H).

TLC: Rf (CH_2Cl_2) = 0.71.

Synthesis of 8a

To **7a** (2.0 g, 2.7 mmol, 1 equiv.) dissolved in DMF (50 mL), were added vanillin (1.4 g, 9.18 mmol, 3.4 equiv.) and Cs_2CO_3 (4.02 g, 12.3 mmol, 4.5 equiv.). The reaction mixture was stirred at 50 °C for 18 hours. It was diluted with ethyl acetate (150 mL), washed with 10% aqueous NaOH (4 x 70 mL), then with distilled water (3 x 70 mL) and dried over $MgSO_4$. Organic solvent was removed under reduced pressure to give **8a** as a white solid (2.1 g, 82%).
Characterization of **8a** was consistent with literature.[8]

^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 9.85 (s, 3H), 7.43-7.41 (m, 6H), 7.04 (d, *J* = 8.7 Hz, 3H), 7.02 (s, 3H), 6.85 (s, 3H), 4.75 (d, *J* = 13.7 Hz, 3H), 4.47-4.35 (m, 12H), 3.90 (s, 9H), 3.74 (s, 9H), 3.55 (d, *J* = 13.7 Hz, 3H).

Synthesis of 8b

To **7b** (1.0 g, 1.3 mmol, 1 equiv.) dissolved in DMF (25 mL), were added vanillin (671 mg, 4.4 mmol, 3.4 equiv.) and Cs_2CO_3 (1.9 g, 5.8 mmol, 4.5 equiv.). The reaction mixture was stirred at 50 °C for 18 hours. It was diluted with ethyl acetate (75 mL), washed with 10% aqueous NaOH (4 x 35 mL), then with distilled water (3 x 35 mL) and dried over $MgSO_4$. Organic solvent was removed under reduced pressure to give **8b** as a white solid (1.17 g, 90%).
Characterization of **8b** was consistent with literature.[9]

^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 9.81 (s, 3H), 7.38-7.36 (m, 6H), 6.97-6.95 (m, 3H), 6.90 (s, 3H), 6.83 (s, 3H), 4.73 (d, *J* = 13.7 Hz, 3H), 4.36-4.13 (m, 12H), 3.88 (s, 9H), 3.73 (s, 9H), 3.50 (d, *J* = 13.7 Hz, 3H), 2.37-2.30 (m, 6H).

Synthesis of 9a

8a (2.0 g, 2.12 mmol, 1 equiv.) was dissolved into a mixture of 50 mL of chloroform/methanol (1/1). $NaBH_4$ (2.4 g, 63.6 mmol, 30 equiv.) was added at 0°C and the reaction mixture was stirred for 2 hours, then for 20 hours at room temperature. Solvents were evaporated and the residue was dissolved in 100 mL of water and extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated and the resulting solid was purified by silica gel column chromatography using $CHCl_3/CH_3OH$ (95/5) as eluent to yield **9a** as a white solid (1.92 g, 92%).
Characterization of **9a** was consistent with literature.[10]

^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 7.00 (s, 3H), 6.90 (d, *J* = 1.8 Hz, 3H), 6.87 (s, 3H), 6.83 (d, *J* = 1.8 Hz, 3H), 6.82 (s, 3H), 4.74 (d, *J* = 13.8 Hz, 3H), 4.61 (d, *J* = 5.6 Hz, 6H), 4.38-4.35 (m, 12H), 3.77 (s, 9H), 3.70 (s, 9H), 3.53 (d, *J* = 13.8 Hz, 3H).

TLC: Rf ($CHCl_3/CH_3OH$: 95/5) = 0.23.

Synthesis of 9b

8b (1.0 g, 1.0 mmol, 1 equiv.) was dissolved into a mixture of 25 mL of chloroform/methanol (1/1). $NaBH_4$ (1.15 g, 30.0 mmol, 30 equiv.) was added at 0°C and the reaction mixture was stirred for 2 hours, then for 20 hours at room temperature. Solvents were evaporated and the residue was dissolved in 50 mL of water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated and the resulting solid was purified by silica gel column chromatography using $CHCl_3/CH_3OH$ (95/5) as eluent to yield **9b** as a white solid (882 mg, 89%).
Characterization of **9b** was consistent with literature.[9]

^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 6.92-6.78 (m, 15H), 4.73 (d, *J* = 13.8 Hz, 3H), 4.62-4.54 (m, 6H), 4.26-4.12 (m, 12H), 3.77 (s, 9H), 3.70 (s, 9H), 3.51 (d, *J* = 13.8 Hz, 3H), 2.32-2.25 (m, 6H).

TLC: Rf ($CHCl_3/CH_3OH$: 95/5) = 0.12.

Synthesis of *anti*-10a (Cryptophane A) and *syn*-10a (Cryptophane B)

9a (100 mg, 102 μmol, 1 equiv.) was dissolved into 100 mL of chloroform/HFIP (1/1). After complete dissolution of **9a**, $KHSO_4$ (10 mg, 73 μmol, 0.7 equiv.) was added. The reaction mixture was stirred for 20 hours. The solvents were evaporated and resulting oil was dissolved in 20 mL of dichloromethane, washed with water (30 mL) and extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated and the resulting solid was purified by silica gel column chromatography using $CHCl_3/CH_3COCH_3$ (90/10) as eluent to yield ***syn*-10a** (54 mg, 60%) and ***anti*-10a** (18 mg, 20%) as white solids.
Characterizations of ***syn*-10a** and ***anti*-10a** were consistent with literature.[11]

***syn*-10a** - ^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 6.76 (s, 6H), 6.68 (s, 6H), 4.60 (d, *J* = 13.7 Hz, 6H), 4.19-4.13 (m, 12 H), 3.80 (s, 18H), 3.40 (d, *J* = 13.7 Hz, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz, 298K) δ 179.6, 146.7, 134.1, 131.6, 120.8, 113.8, 69.3, 55.7, 36.2.

TLC: Rf ($CHCl_3/CH_3COCH_3$: 90/10) = 0.62.

***anti*-10a** - ^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 6.78 (s, 6H), 6.68 (s, 6H), 4.58 (d, *J* = 13.7 Hz, 6H), 4.31-4.26 (m, 6 H), 3.95-3.91 (m, 6H), 3.79 (s, 18H), 3.40 (d, *J* = 13.7 Hz, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz, 298K) δ 150.2, 146.2, 134.9, 131.7, 122.6, 114.3, 70.3, 55.8, 36.2.

TLC: Rf ($CHCl_3/CH_3COCH_3$: 90/10) = 0.32.

Synthesis of *anti*-10b (Cryptophane E) and *syn*-10b (Cryptophane F)

9b (200 mg, 202 μmol, 1 equiv.) was dissolved into 200 mL of chloroform/HFIP (1/1). After complete dissolution of **9b**, $KHSO_4$ (20 mg, 146 μmol, 0.7 equiv.) was added. The reaction mixture was stirred for 20 hours. The solvents were evaporated and resulting oil was dissolved in 40 mL of dichloromethane, washed with water (60 mL) and extracted with dichloromethane (2 x 40 mL). The combined organic layers were dried over $MgSO_4$ and evaporated and the resulting solid was purified by silica gel column chromatography using $CHCl_3/CH_3COCH_3$ (90/10) as eluent to yield ***anti*-10b** (75 mg, 40%) and ***syn*-10b** (47 mg, 25%) as white solids.
Characterizations of ***anti*-10b** and ***syn*-10b** were consistent with literature.[9,12]

***anti*-10b** - ^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 6.69 (s, 6H), 6.61 (s, 6H), 4.67 (d, *J* = 13.7 Hz, 6H), 4.07-4.04 (m, 6H), 3.91-3.85 (m, 6H), 3.83 (s, 9H), 4.43 (d, *J* = 13.7 Hz, 6H), 2.31-2.28 (m, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz, 298K) δ 147.2, 147.1, 131.1, 131.1, 112.3, 112.2, 63.7, 55.7, 36.1, 29.7.

TLC: Rf ($CHCl_3/CH_3COCH_3$: 90/10) = 0.57.

***syn*-10b** - ^{1}H NMR ($CDCl_3$, 300 MHz, 298K) δ 6.72 (s, 6H), 6.67 (s, 6H), 4.60 (d, *J* = 13.7 Hz, 6H), 4.09-4.04 (m, 6 H), 3.90-3.76 (m, 6H), 3.76 (s, 18H), 3.41 (d, *J* = 13.7 Hz, 6H), 2.36-2.29 (m, 3H), 2.00-1.94 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, 298K) δ 149.0, 147.3, 133.3, 131.9, 118.3, 113.8, 69.2, 55.9, 36.1, 30.4.

TLC: Rf ($CHCl_3/CH_3COCH_3$: 90/10) = 0.13.

Influence of HFIP on the cyclisation percussor 9a

A solution of precursor **9a** (3 mM in $CDCl_3$, 600 μL) was titrated in NMR tubes with aliquots of a concentrated solution of HFIP (30 mM in $CDCl_3$). The shifts Δδ of the precursor's proton signals at 6.907, 6.872 and 6.831 ppm of precursor **9a** and proton at 4.397 ppm of HFIP were measured after each addition and plotted as a function of the number of equivalents of HFIP. Association constant Ka was obtained by nonlinear leastsquares fitting of these plots using the Bindfit[13].

3. NMR spectra

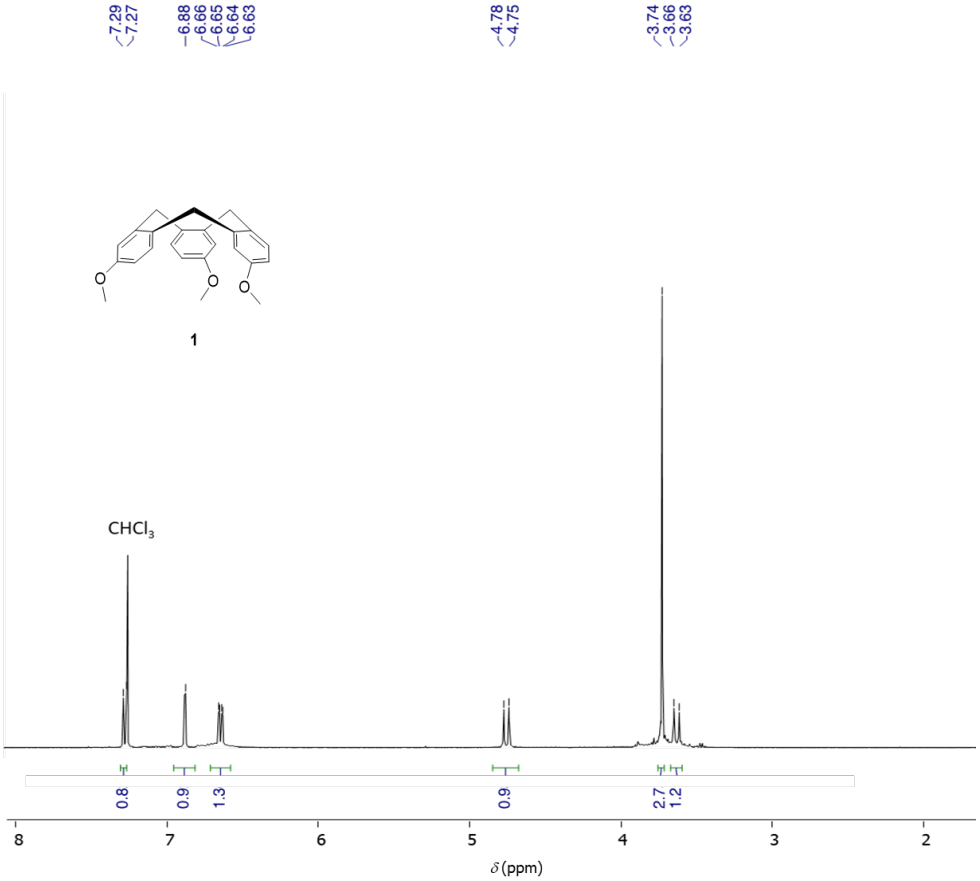


Figure S1. ^{1}H NMR spectrum of **1** ($CDCl_3$, 300 MHz, 298 K).

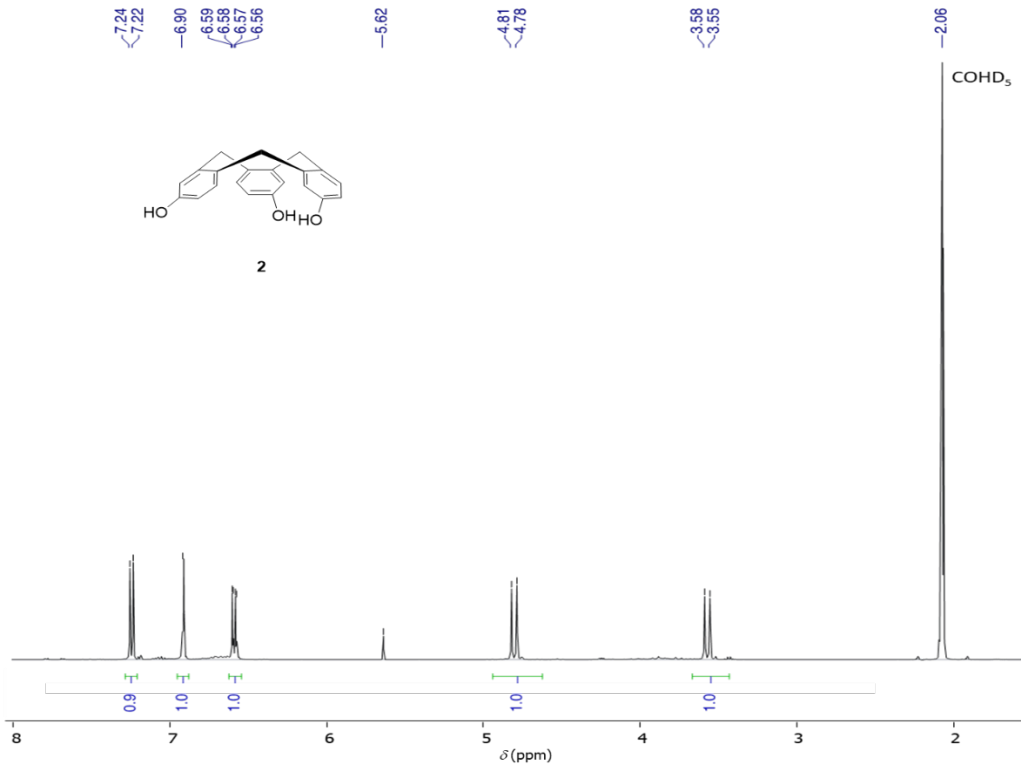


Figure S2. ^{1}H NMR spectrum of **2** (acetone-d_6, 300 MHz, 298 K).

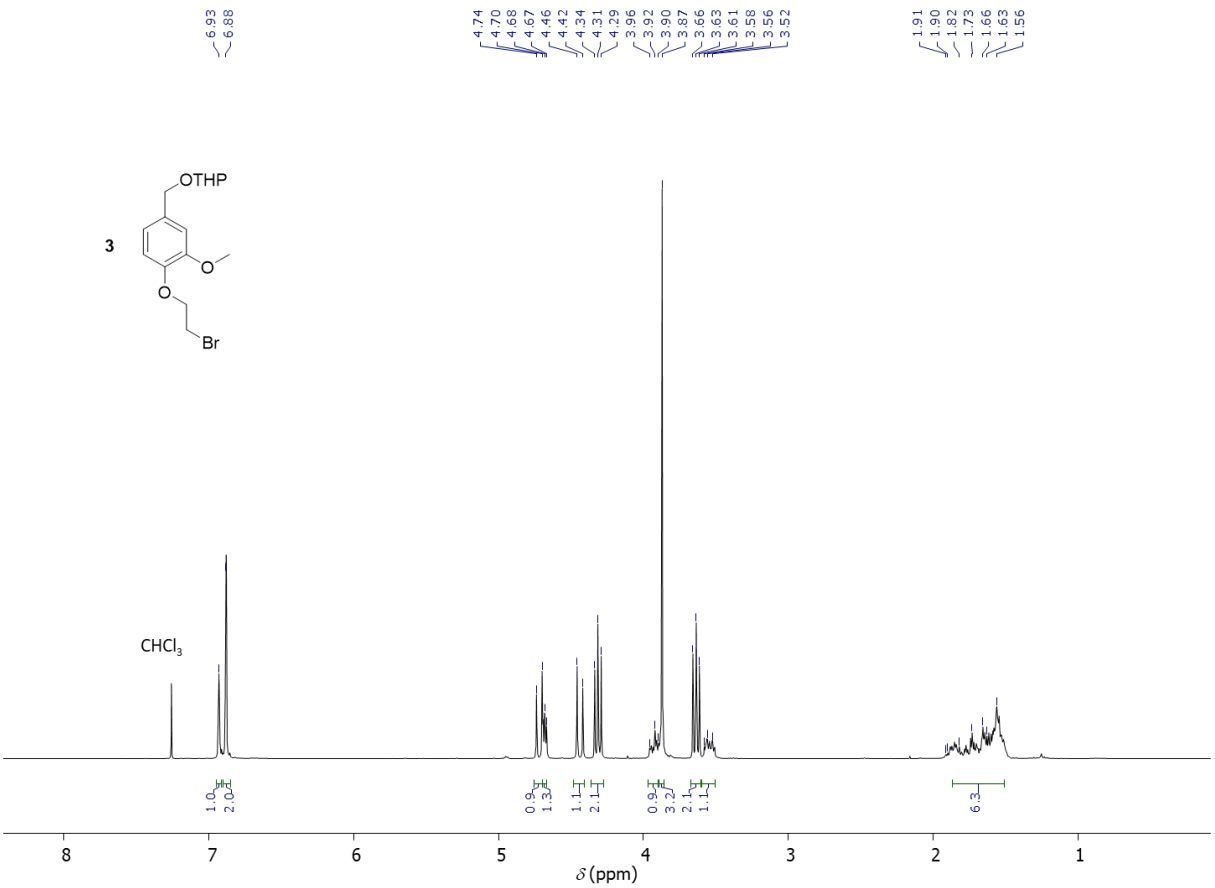


Figure S3. ^{1}H NMR spectrum of **3** ($CDCl_3$, 300 MHz, 298 K).

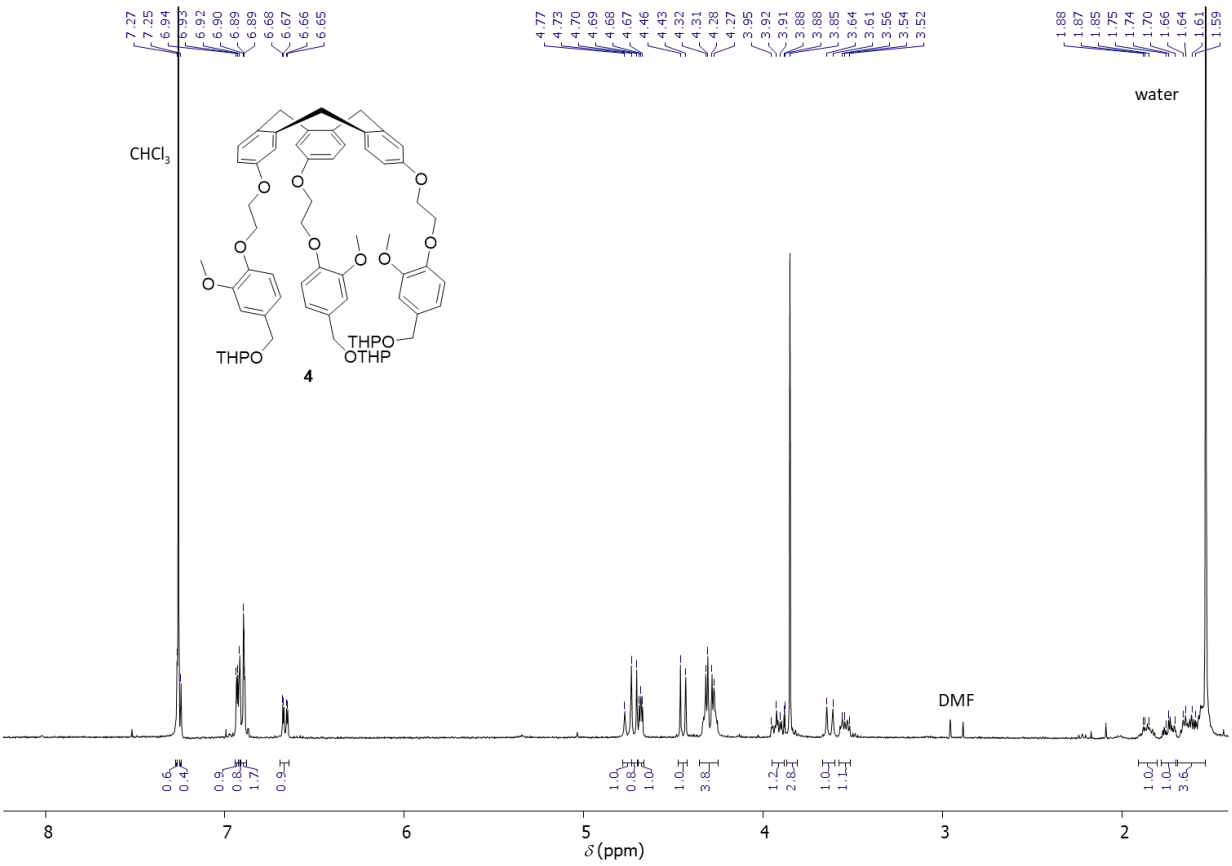


Figure S4. ^{1}H NMR spectrum of **4** ($CDCl_3$, 300 MHz, 298 K).

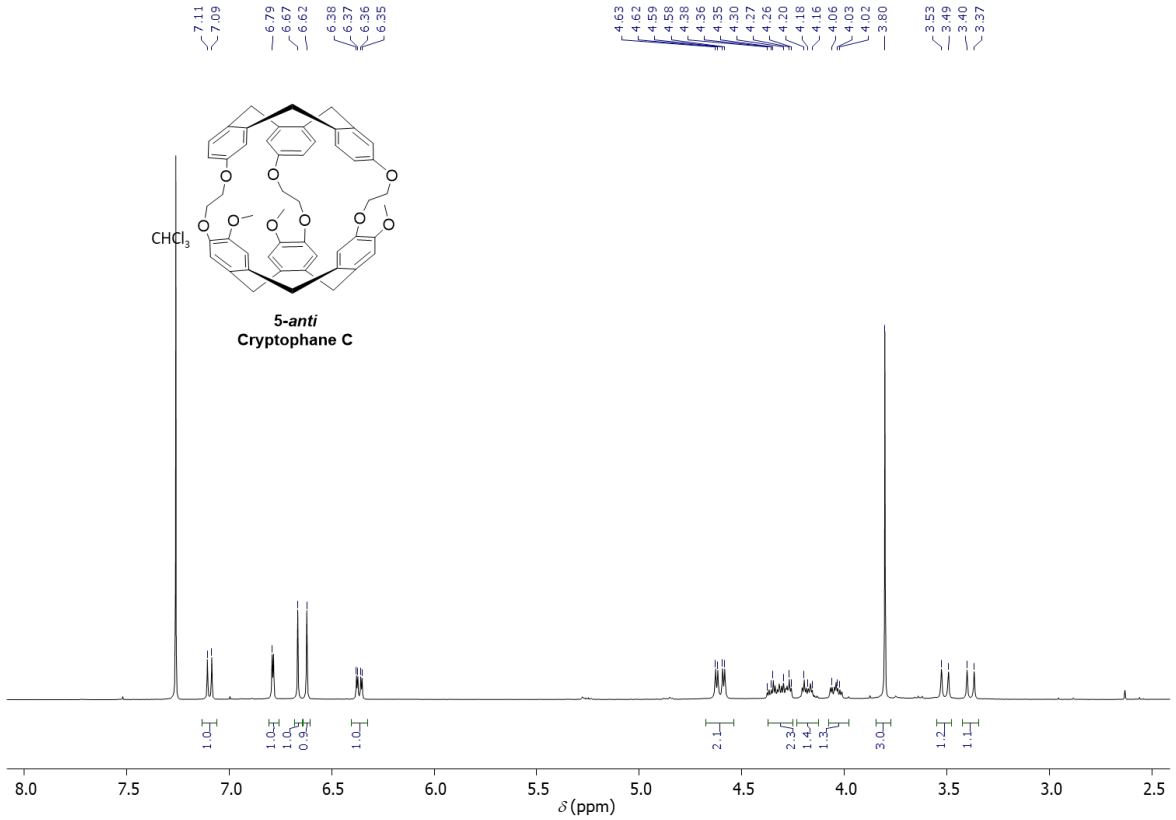


Figure S5. ^{1}H NMR spectrum of ***anti*-5** ($CDCl_3$, 300 MHz, 298 K).

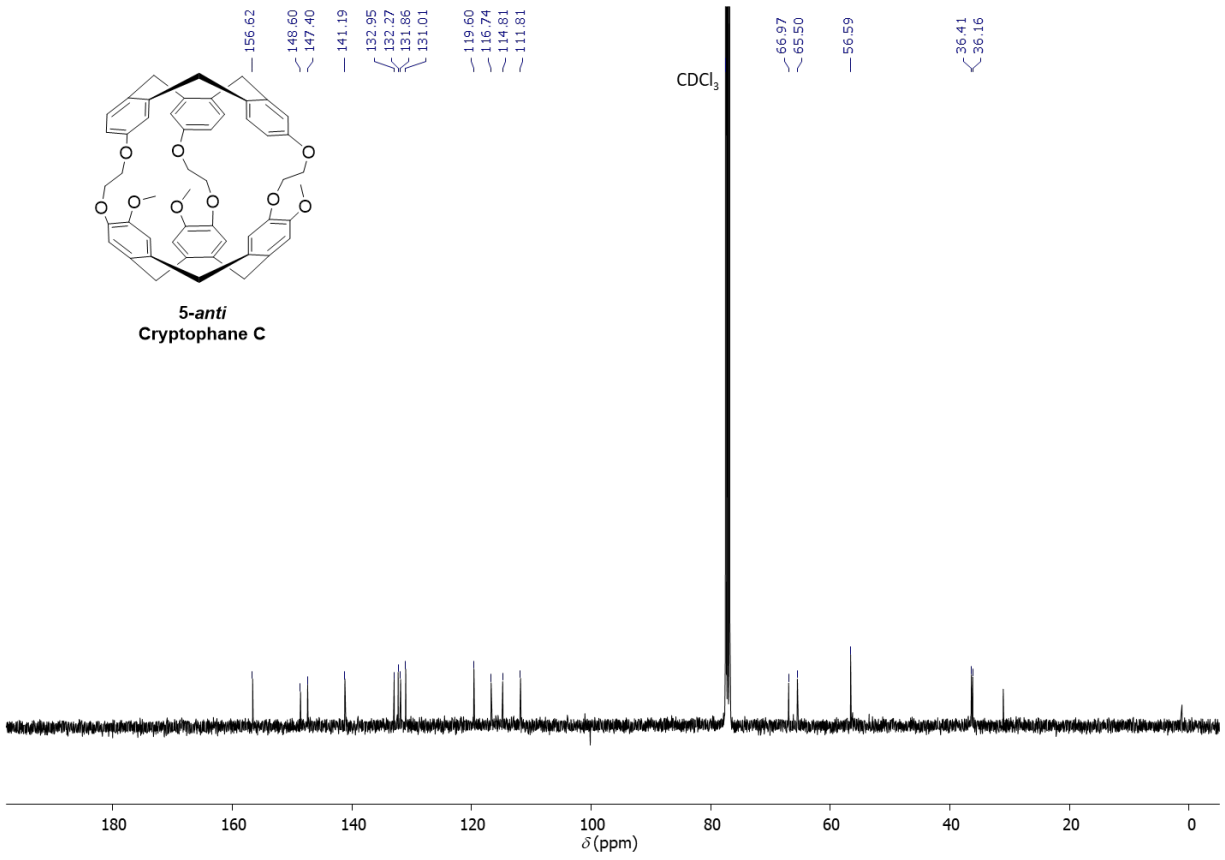


Figure S6. ^{13}C NMR spectrum of ***anti*-5** ($CDCl_3$, 75 MHz, 298 K).

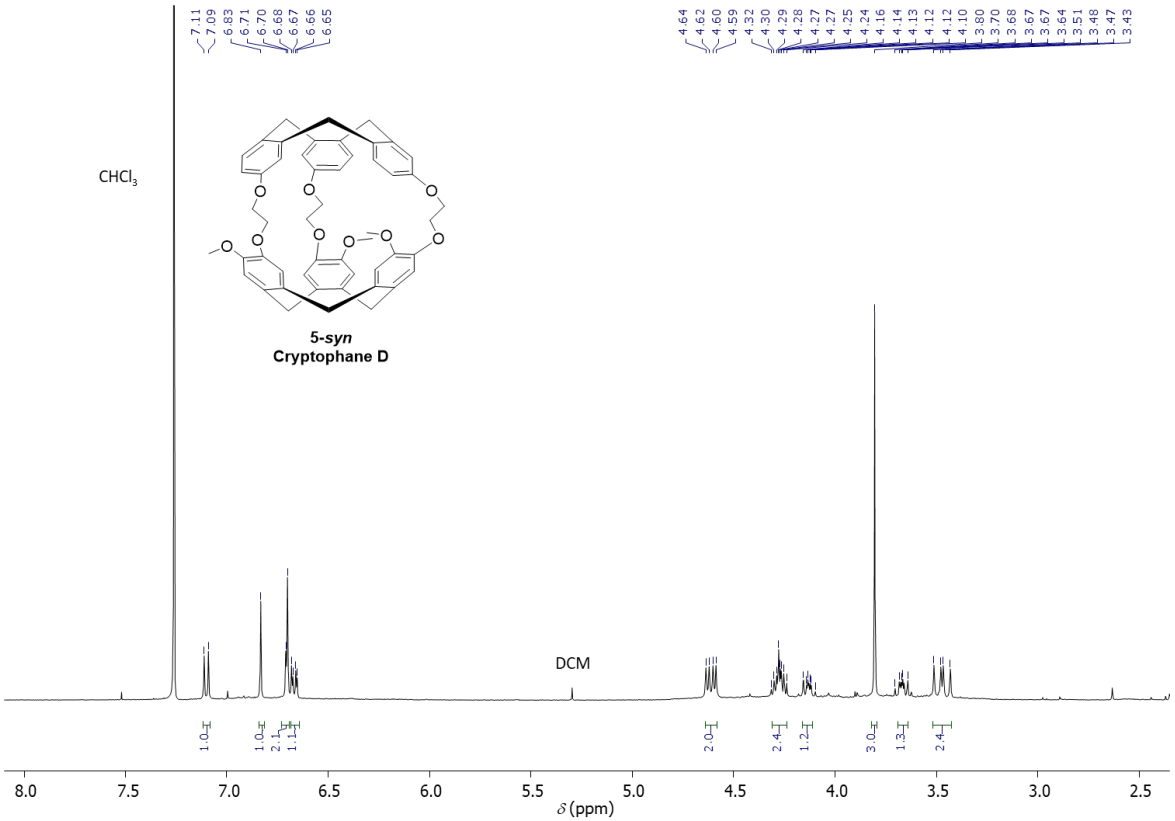


Figure S7. ^{1}H NMR spectrum of ***syn*-5** ($CDCl_3$, 300 MHz, 298 K).

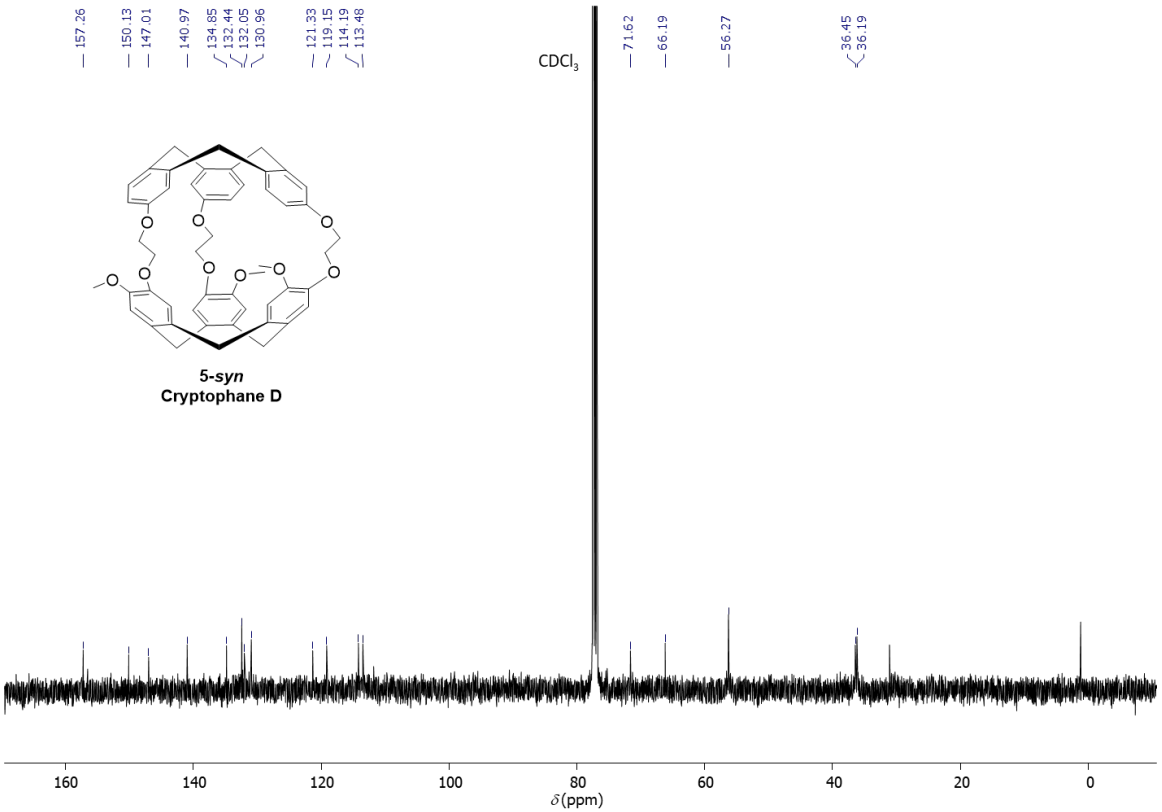


Figure S8. ^{13}C NMR spectrum of ***syn*-5** ($CDCl_3$, 75 MHz, 298 K).

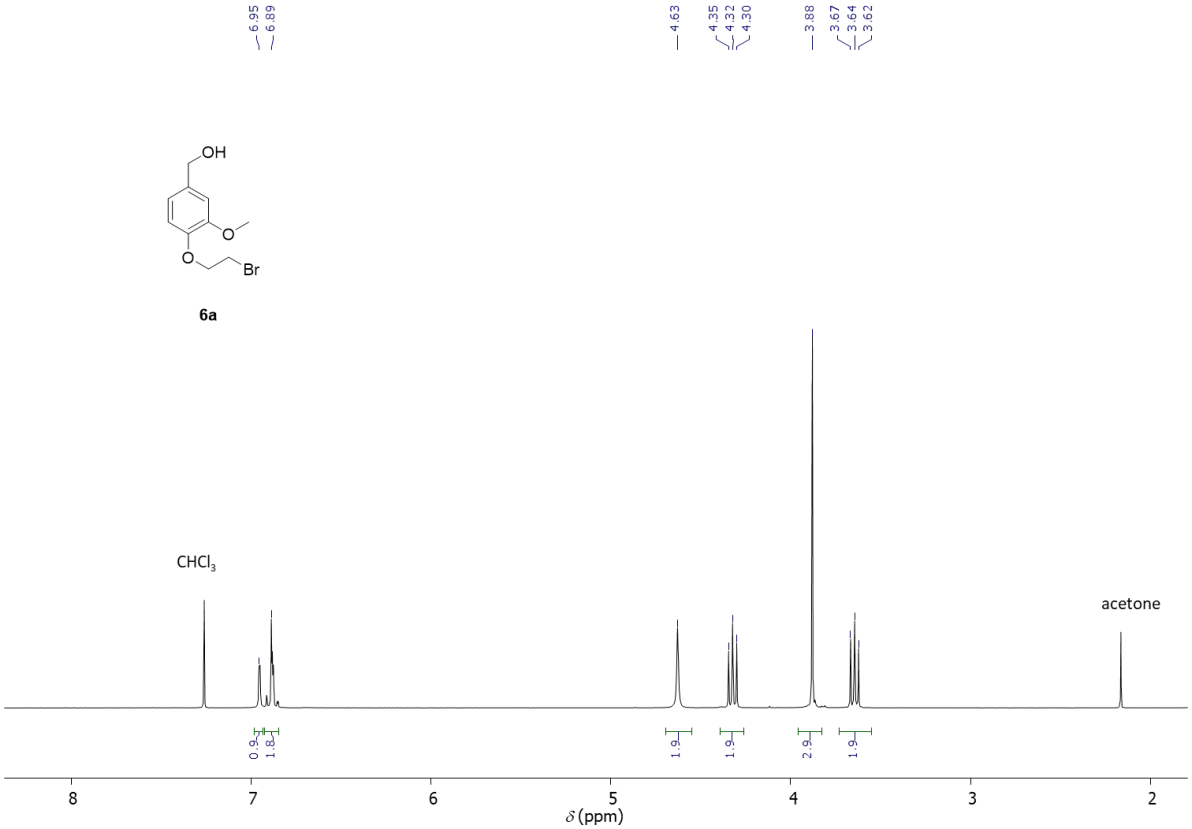


Figure S9. ^{1}H NMR spectrum of **6a** ($CDCl_3$, 300 MHz, 298 K).

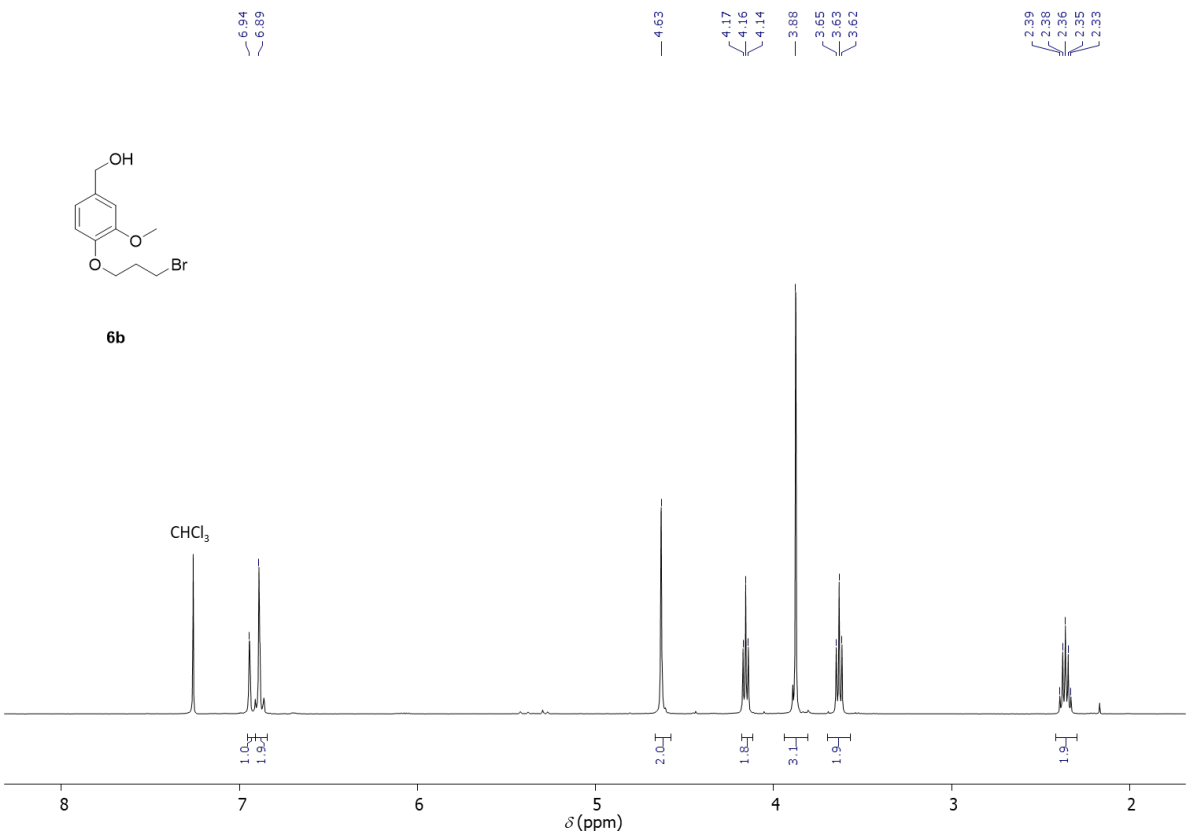


Figure S10. ^{1}H NMR spectrum of **6b** ($CDCl_3$, 300 MHz, 298 K).

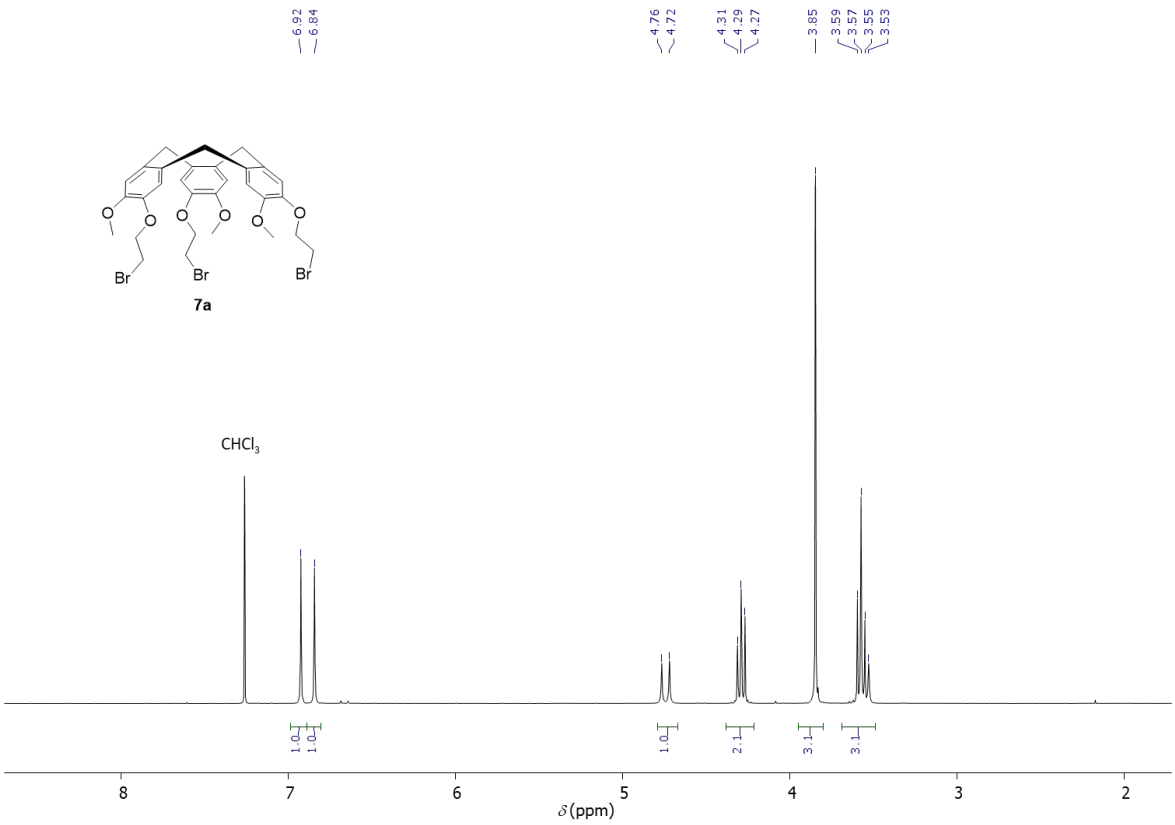


Figure S11. ^{1}H NMR spectrum of **7a** ($CDCl_3$, 300 MHz, 298 K).

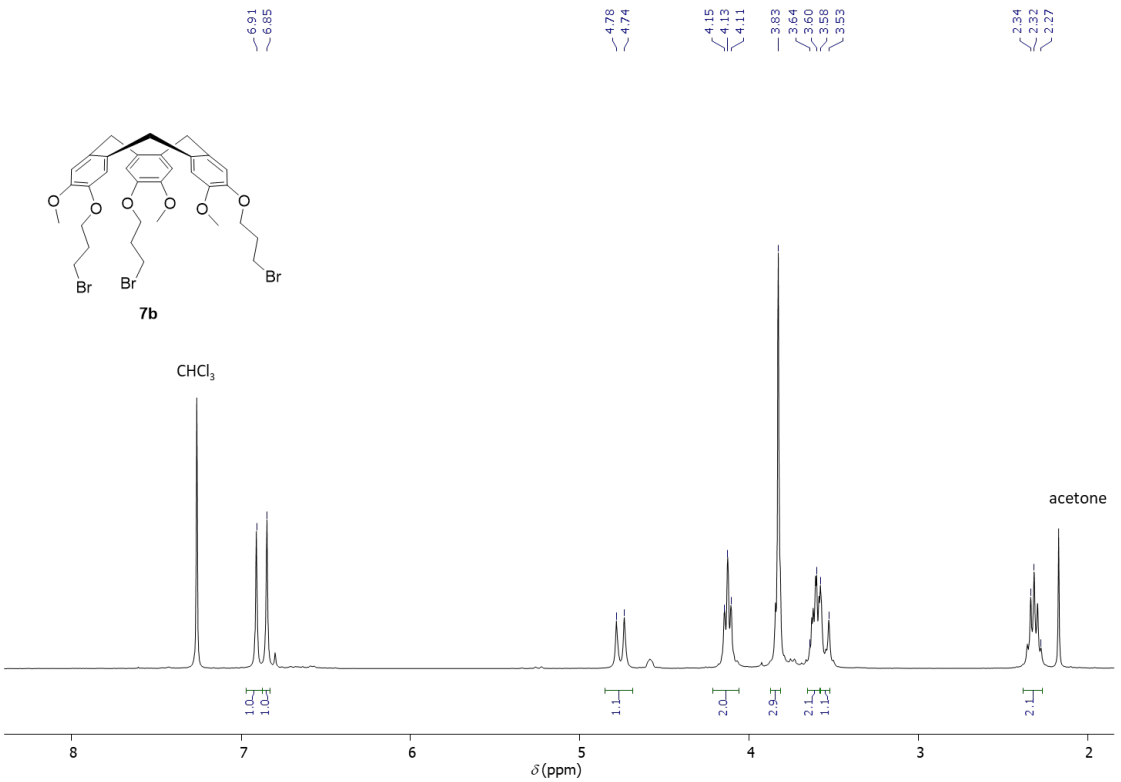


Figure S12. ^{1}H NMR spectrum of **7b** ($CDCl_3$, 300 MHz, 298 K).

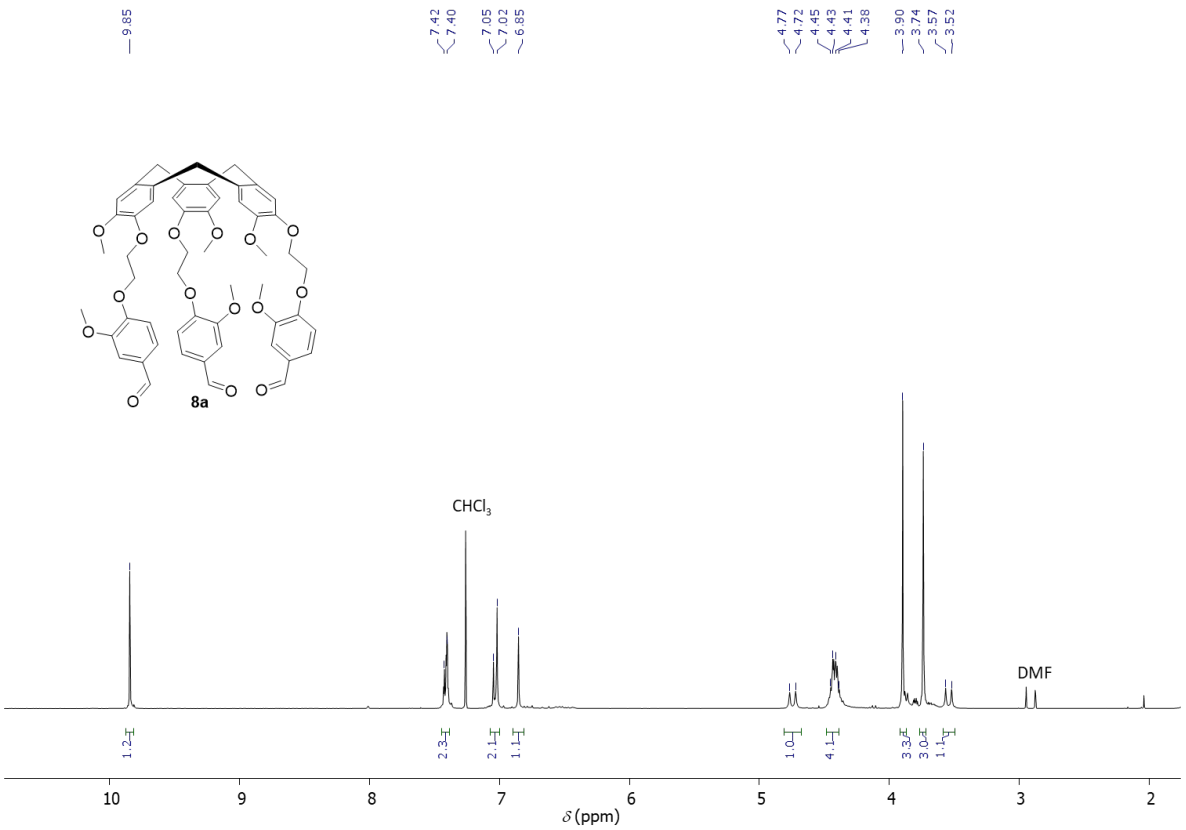


Figure S13. ^{1}H NMR spectrum of **8a** ($CDCl_3$, 300 MHz, 298 K).

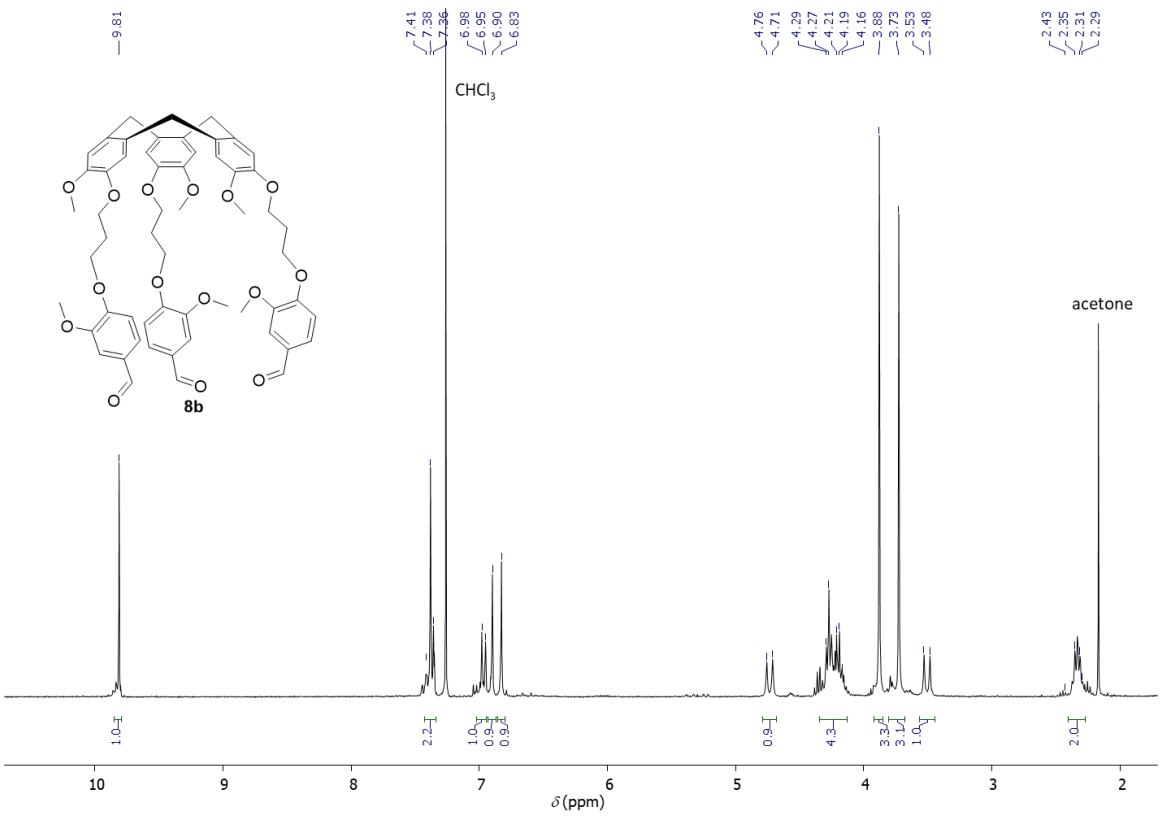


Figure S14. ^{1}H NMR spectrum of **8b** ($CDCl_3$, 150 MHz, 298 K).

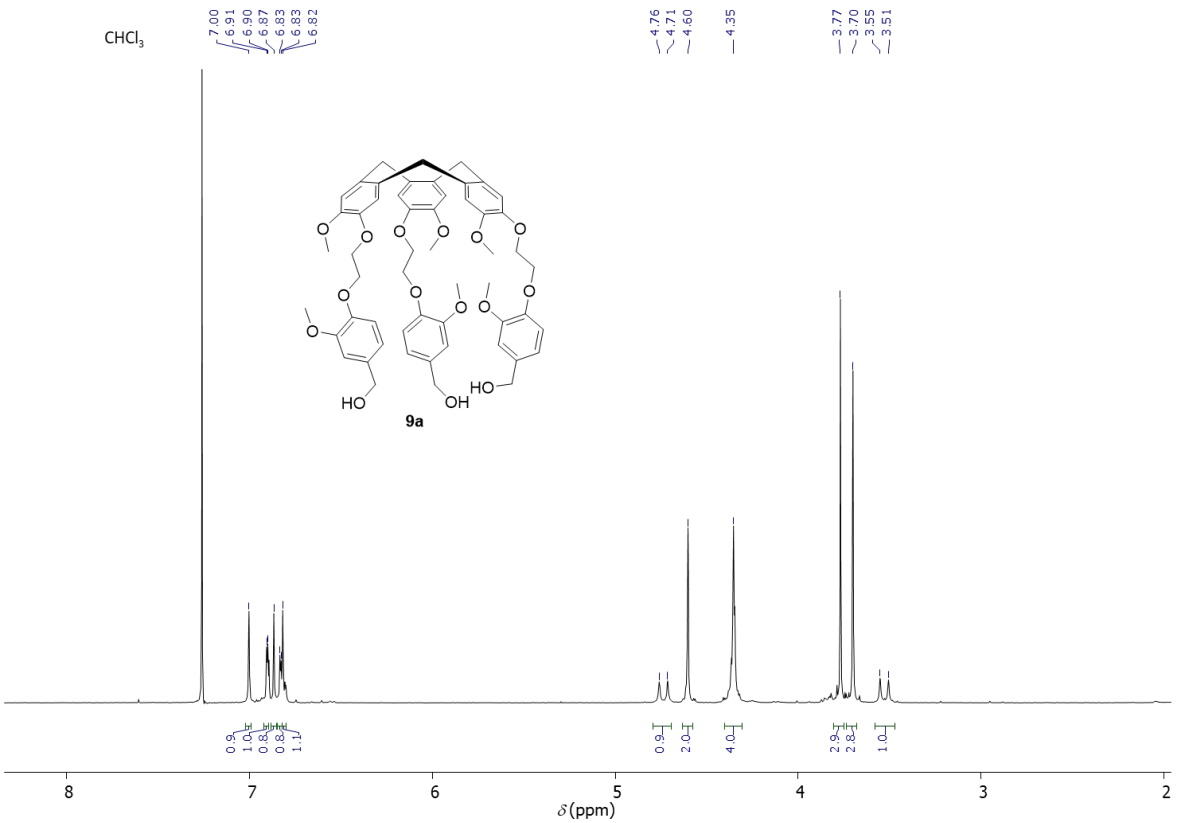


Figure S15. ^{1}H NMR spectrum of **9a** ($CDCl_3$, 300 MHz, 298 K).

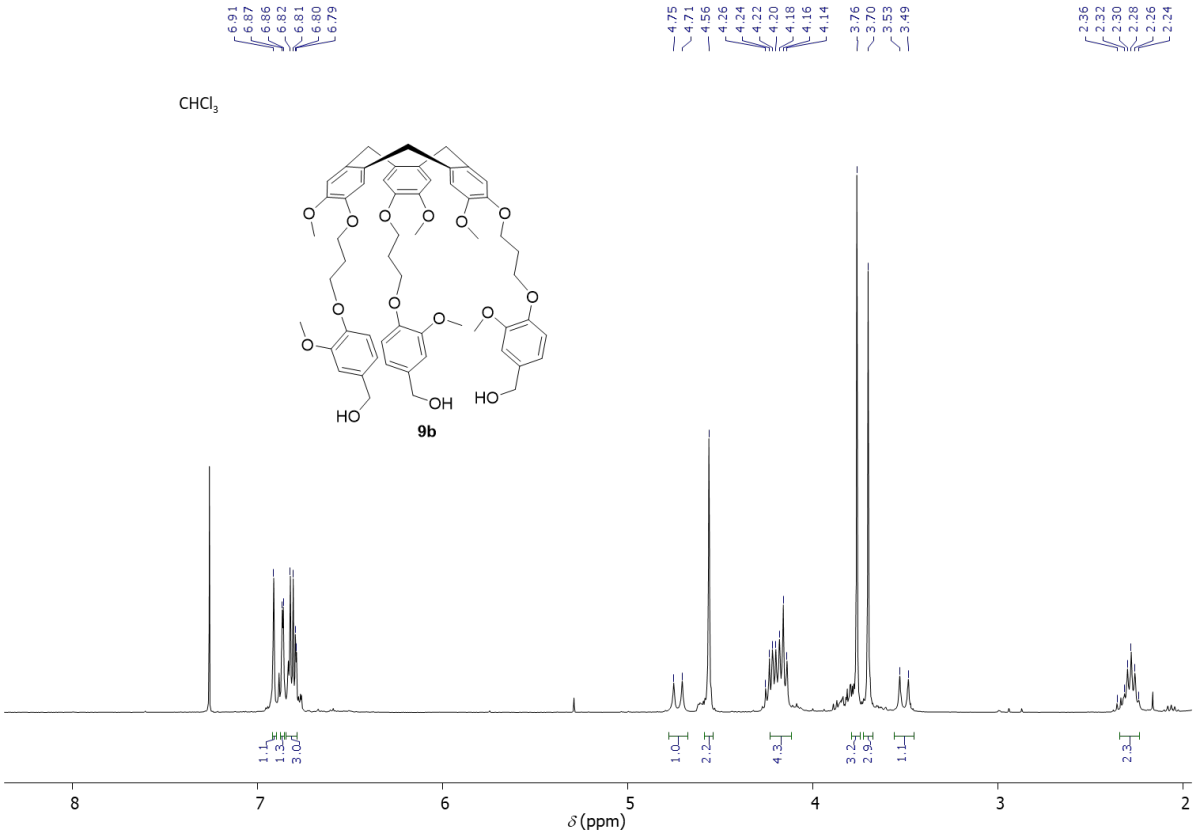


Figure S16. ^{1}H NMR spectrum of **9b** ($CDCl_3$, 300 MHz, 298 K).

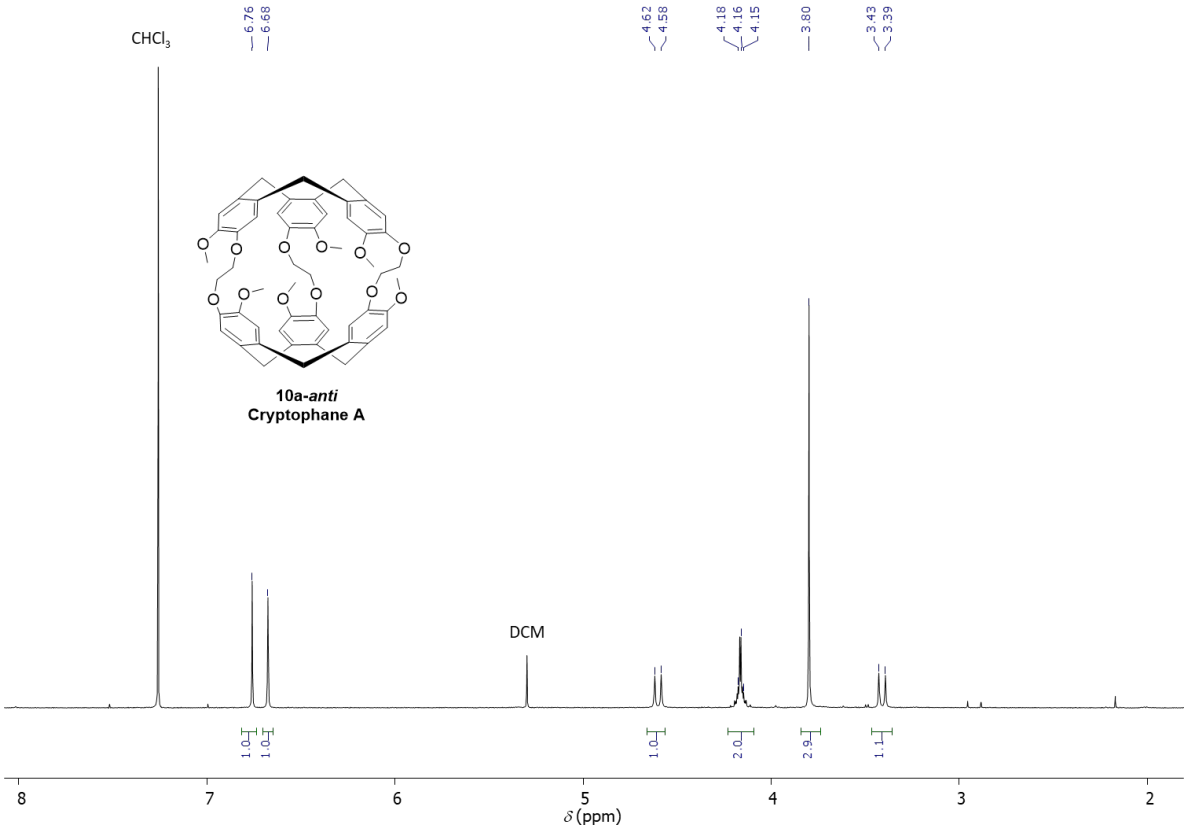


Figure S17. ^{1}H NMR spectrum of ***anti*-10a** ($CDCl_3$, 300 MHz, 298 K).

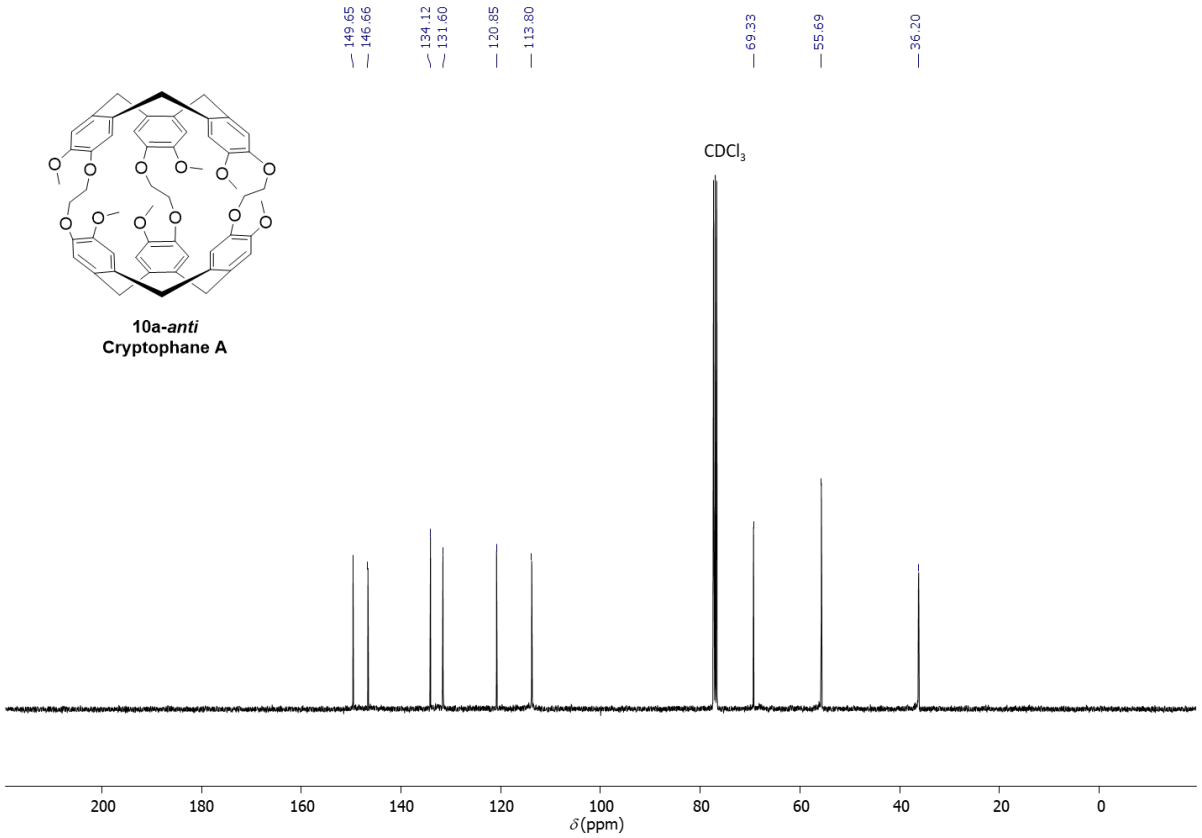


Figure S18. ^{13}C NMR spectrum of ***anti*-10a** ($CDCl_3$, 75 MHz, 298 K).

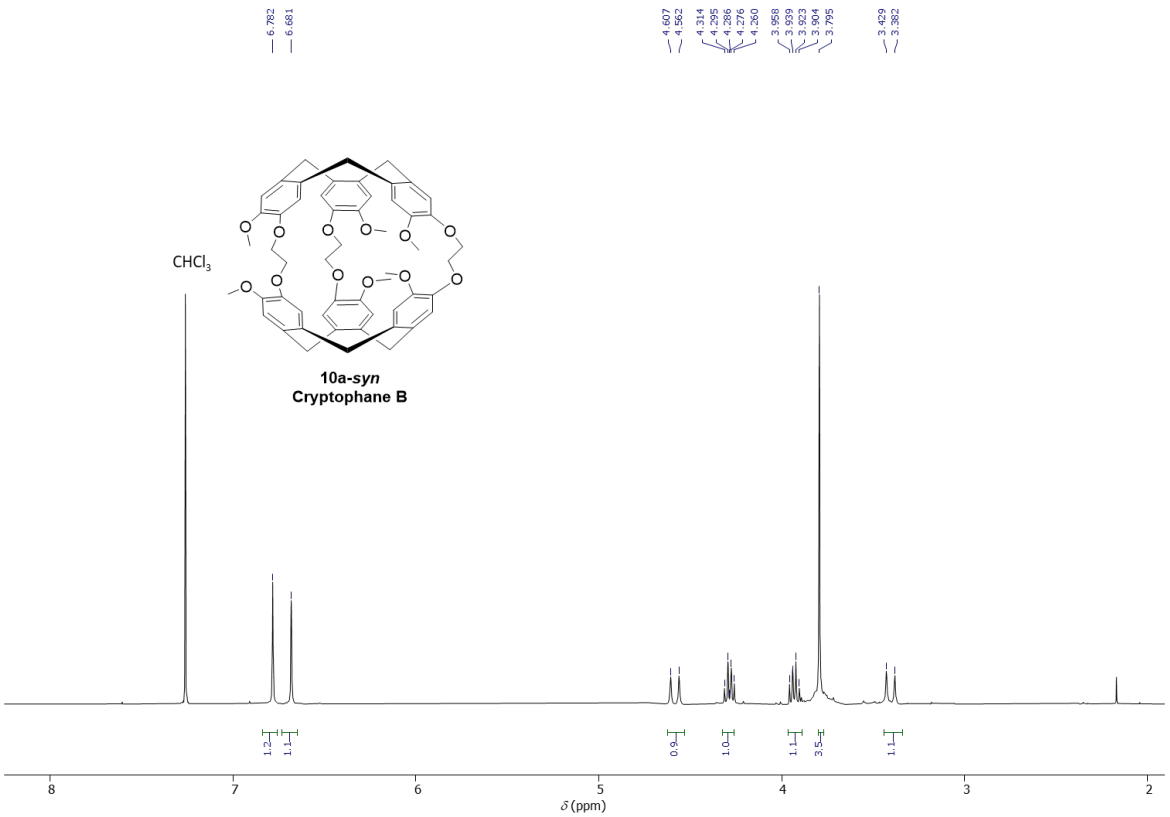


Figure S19. ^{1}H NMR spectrum of ***syn*-10a** ($CDCl_3$, 300 MHz, 298 K).

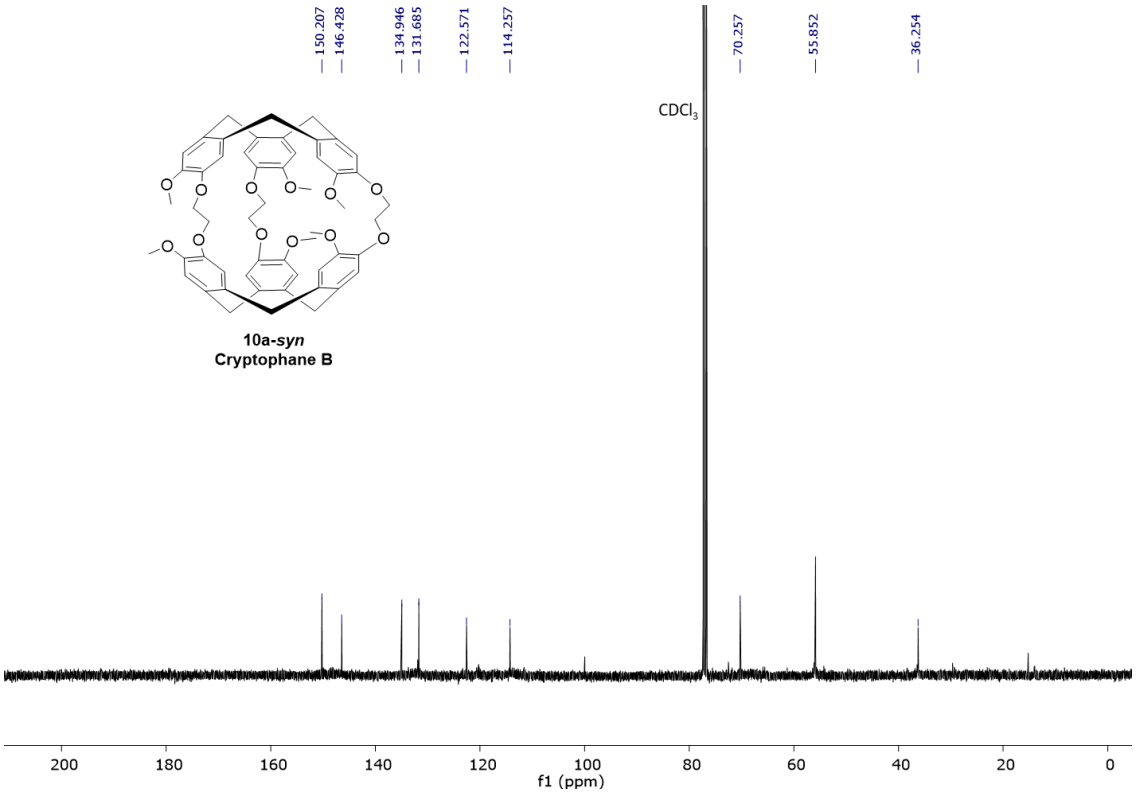


Figure S20. ^{13}C NMR spectrum of ***syn*-10a** ($CDCl_3$, 75 MHz, 298 K).

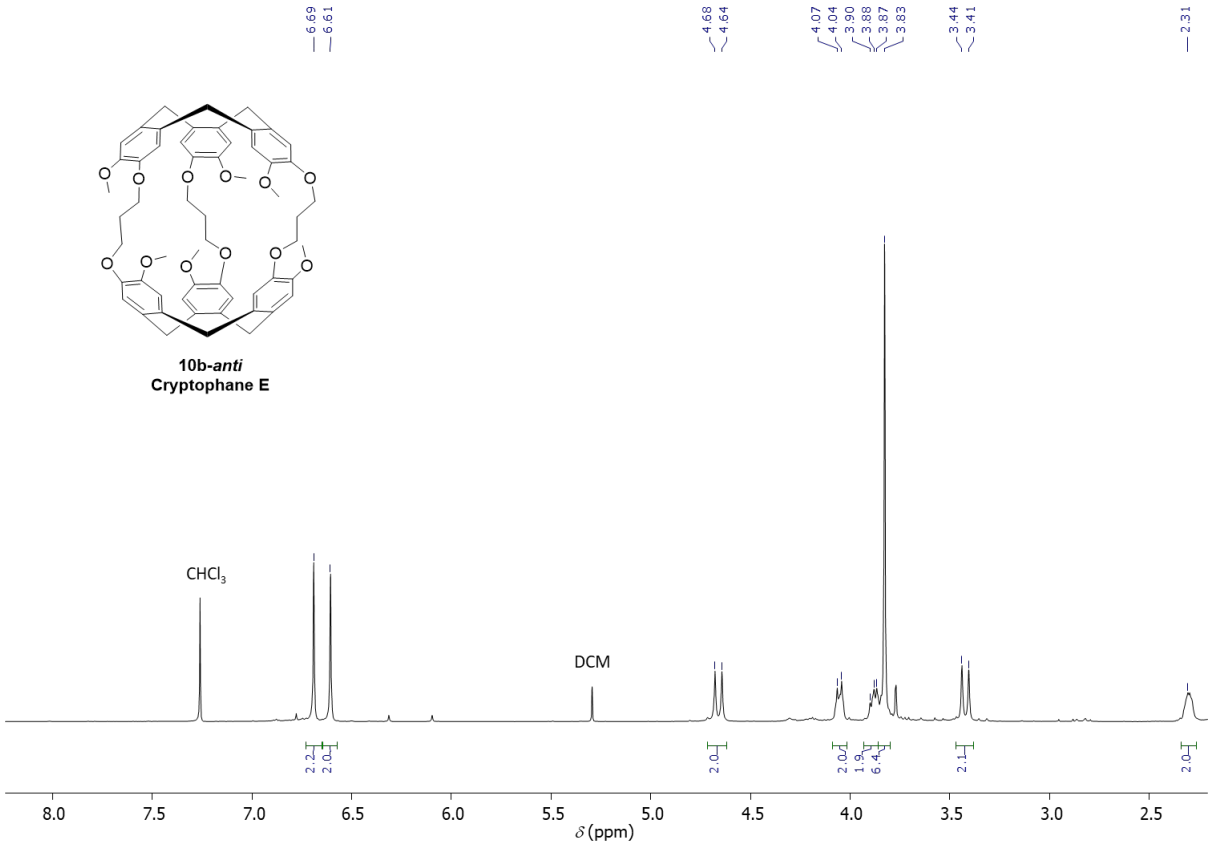


Figure S21. ^{1}H NMR spectrum of ***anti*-10b** ($CDCl_3$, 300 MHz, 298 K).

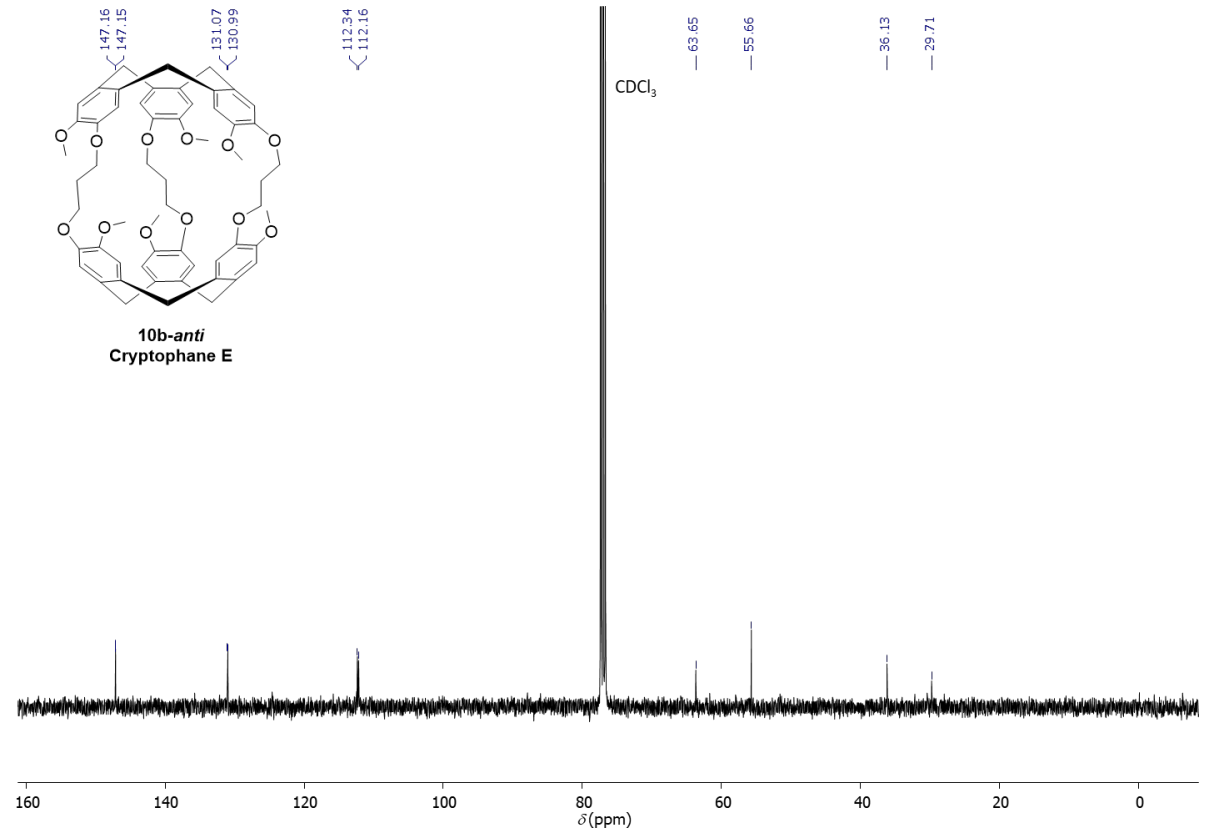


Figure S22. ^{13}C NMR spectrum of ***anti*-10b** ($CDCl_3$, 75 MHz, 298 K).

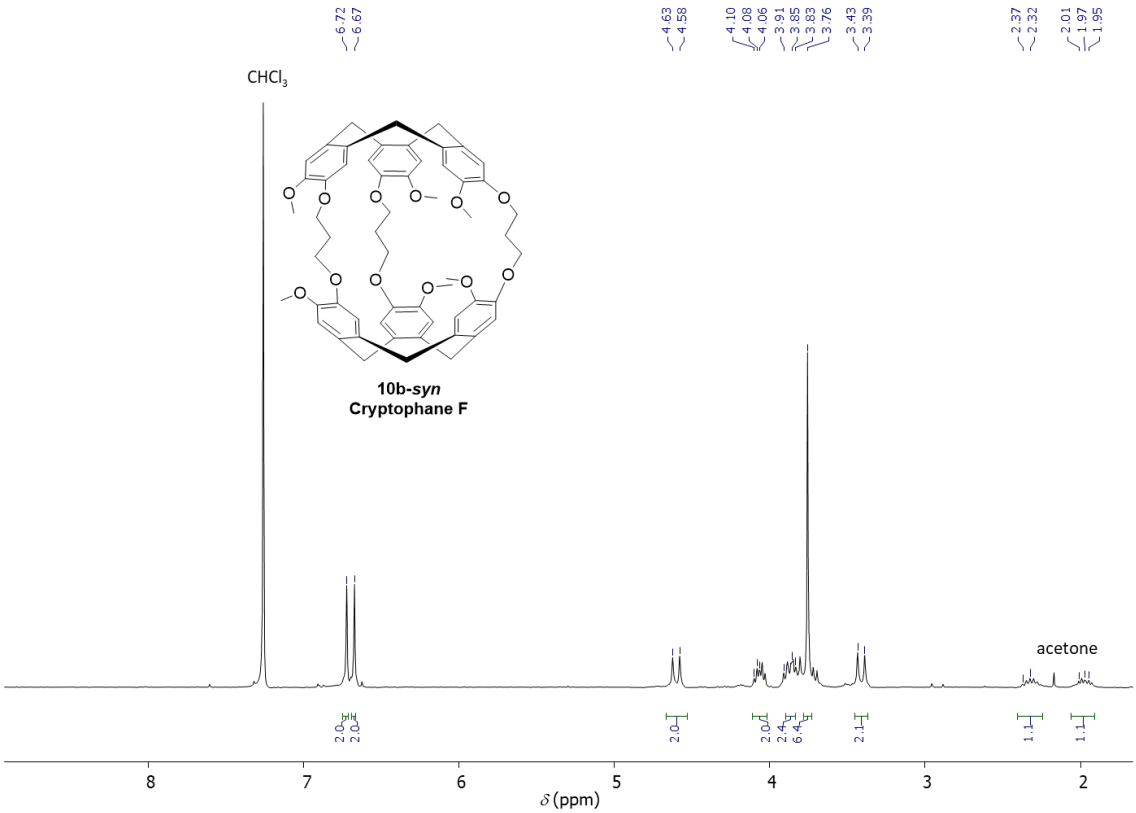


Figure S.23. ^{1}H NMR spectrum of ***syn*-10b** ($CDCl_3$, 300 MHz, 298 K).

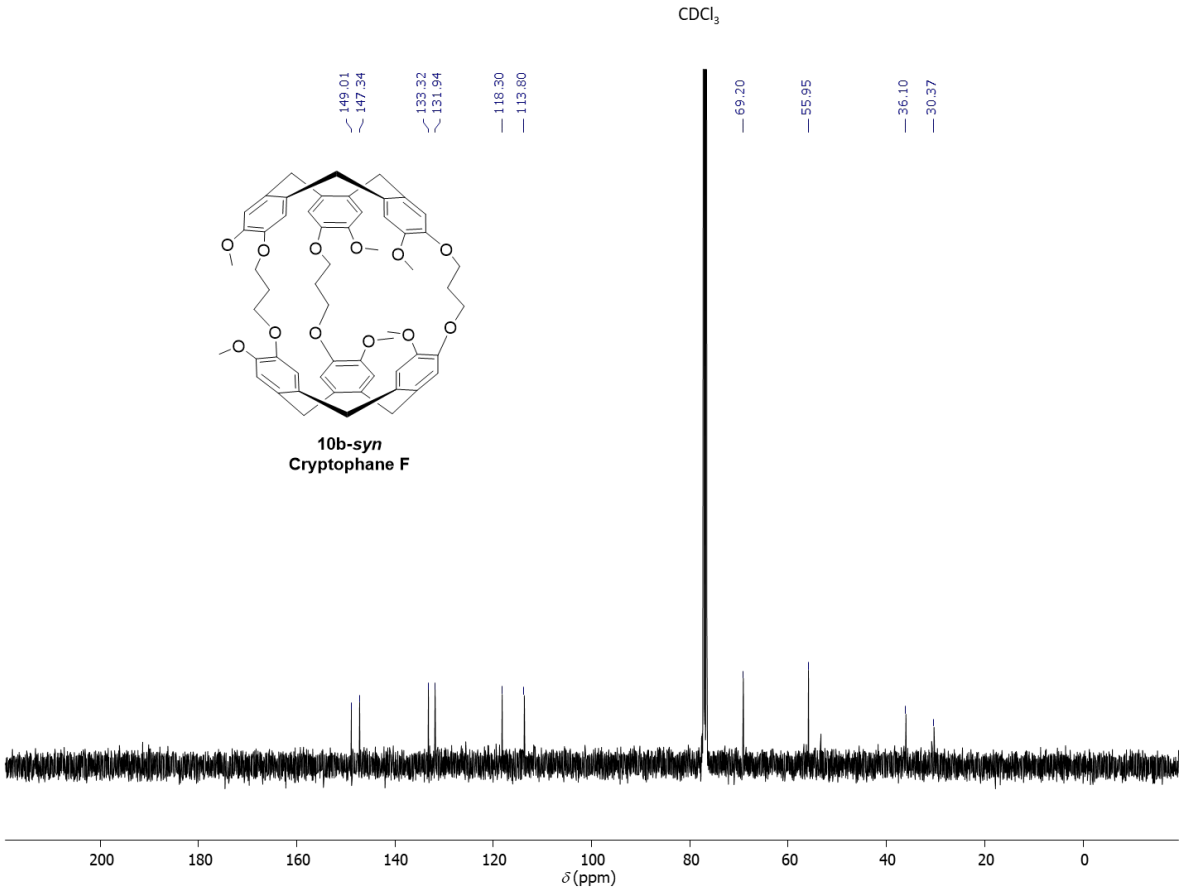


Figure S24. ^{13}C NMR spectrum of ***syn*-10b** ($CDCl_3$, 75 MHz, 298 K).

4. Influence of HFIP on the cyclisation precursor 9a

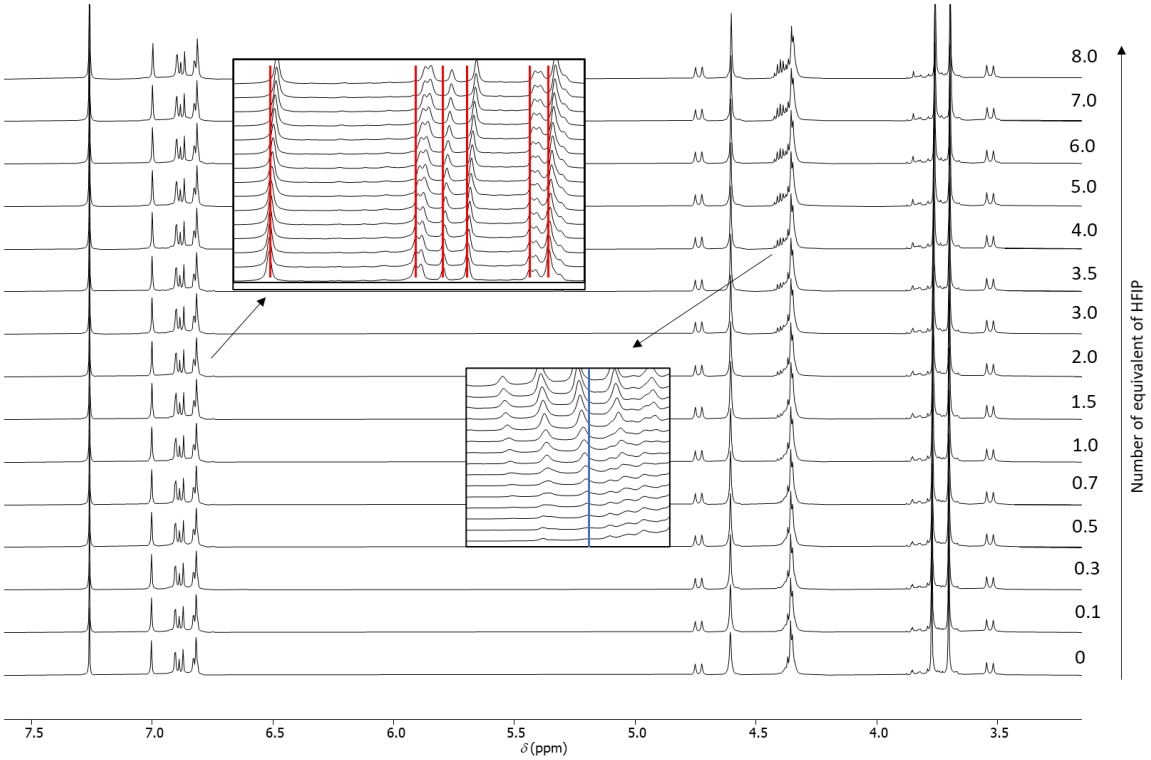
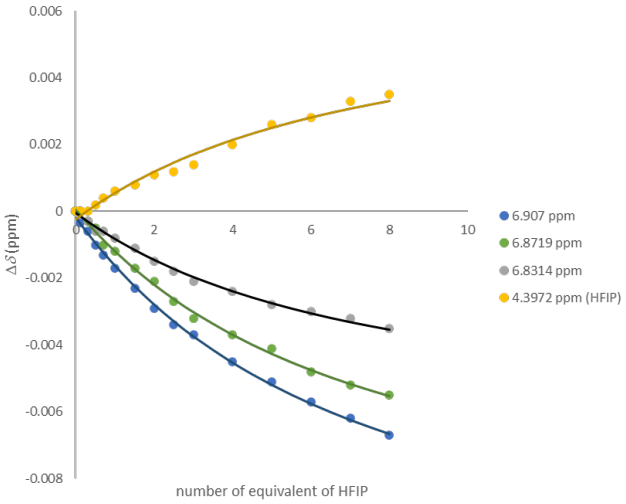


Figure S25. ^{1}H NMR spectra ($CDCl_3$, 500 MHz, 298 K) of precursor **9a** upon progressive addition of HFIP.

(a)



(b)

K affinity (M^{-1})	K error (%)	RMS	Covariance
51	2	1.1×10^{-4}	2.1×10^{-3}

Figure S26. (a) ^{1}H NMR titration curves ($CDCl_3$, 500 MHz, 298 K) of precursor **9a** (3mM) upon progressive addition of HFIP. The chemical induced shifts $\Delta\delta$ of aromatic protons at 6.907, 6.872 and 6.831 ppm of precursor **9a** and proton at 4.397 ppm of HFIP were used. (b) Table gathering data obtained after the affinity constant determination.

5. References

1 F. R. Bissegger, M. Neuburger and K. Tiefenbacher, *Supramolecular Chemistry*, 2020, **32**, 320–324.
2 T. Traoré, L. Delacour, N. Kotera, G. Merer, D.-A. Buisson, C. Dupont and B. Rousseau, *Org. Process Res. Dev.*, 2011, **15**, 435–437.
3 T. Brotin, V. Roy and J.-P. Dutasta, *J. Org. Chem.*, 2005, **70**, 6187–6195.
4 J. Canceill, L. Lacombe and A. Collet, *J. Am. Chem. Soc.*, 1985, **107**, 6993–6996.
5 H. M. Chawla and R. Shrivastava, *Journal of Chemical Research*, 2008, **2008**, 347–353.
6 O. Taratula, P. A. Hill, Y. Bai, N. S. Khan and I. J. Dmochowski, *Org. Lett.*, 2011, **13**, 1414–1417.
7 P. Satha, G. Illa, A. Ghosh and C. S. Purohit, *RSC Adv.*, 2015, **5**, 74457–74462.
8 B. Chatelet, E. Payet, O. Perraud, P. Dimitrov-Raytchev, L.-L. Chapellet, V. Dufaud, A. Martinez and J.-P. Dutasta, *Org. Lett.*, 2011, **13**, 3706–3709.
9 J. Canceill, A. Collet, G. Gottarelli and P. Palmieri, *J. Am. Chem. Soc.*, 1987, **109**, 6454–6464.
10 J. Gabard and A. Collet, *J. Chem. Soc., Chem. Commun.*, 1981, 1137–1139.
11 T. Brotin, E. Jeanneau, P. Berthault, E. Léonce, D. Pitrat and J.-C. Mulatier, *J. Org. Chem.*, 2018, **83**, 14465–14471.
12 A. Collet, J.-P. Dutasta, B. Lozach and J. Canceill, in *Supramolecular Chemistry I — Directed Synthesis and Molecular Recognition*, eds. J. Canceill, J.-C. Chambron, A. Collet, Ch. Dietrich-Buchecker, H. D. Durst, J.-P. Dutasta, F. H. Kohnke, B. Lozach, J.-P. Mathias, S. Misumi, J.-P. Sauvage, J. F. Stoddart, D. A. Tomalia and S. C. Zimmerman, Springer, Berlin, Heidelberg, 1993, pp. 103–129.
13 D. B. Hibbert and P. Thordarson, *Chem. Commun.*, 2016, **52**, 12792–12805.