Supplementary Information

Synthesis of Enantiopure, Trisubstituted Cryptophane-A Derivatives

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Content:

General Methods

^{1}H NMR (360 and 500 MHz) and ^{13}C NMR (90 and 125 MHz) spectra were obtained on Bruker DMX 360 and AMX 500 spectrometers at the University of Pennsylvania NMR facility and were recorded at room temperature in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6) unless otherwise noted. The ^{1}H and ^{13}C NMR spectra were referenced to the central

line of the residual solvent. ^{1}H NMR and ^{13}C NMR chemical shifts (δ) are given in parts per million (ppm) and reported to a precision of ± 0.01 and ± 0.1 ppm, respectively. Proton coupling constants (J) are given in Hz and reported to a precision of ± 0.1 Hz. Column chromatography was performed using silica gel (60 Å pore size, 40-75 μm particle size) from Sorbent Technologies. Thin layer chromatography (TLC) was performed using silica gel plates (60 Å pore size, Whatman) with UV light at 254 nm as the detection method. High resolution mass spectrometry (HRMS) data were obtained using electrospray ionization (ESI) mass spectrometry on a Micromass Autospec at the Mass Spectrometry Center in the Chemistry Department at the University of Pennsylvania. Electronic circular dichroism (ECD) spectra were recorded at room temperature on a Chirascan™ Circular Dichroism Spectrometer using cells with a pathlength of 0.1 cm. UV-visible spectra were measured using a diode-array Agilent 89090A spectrophotometer.

Hyperpolarized ^{129}Xe NMR spectroscopy

We utilized an in-house ^{129}Xe hyperpolarizer based on the IGI.Xe.2000 system made by the former Nycomed-Amersham (now GE). Hyperpolarized gas supply (Concorde Gases) was a mixture of 89% N_2, 10% He, and 1% natural abundance Xe (29.4% ^{129}Xe). ^{129}Xe nuclei were hyperpolarized to 10-15% after being cryogenically separated, accumulated, thawed, and collected in degassed airtight NMR tubes (CAV5, New Era).[1] This traps ~2 atm of hyperpolarized Xe in the tube. After hyperpolarized Xe was retrieved, NMR tubes were shaken vigorously to mix Xe with cryptophane solutions.

All ^{129}Xe NMR measurements were made on a 500 MHz Bruker BioDRX NMR spectrometer at the University of Pennsylvania NMR Facility. RF pulse frequency for ^{129}Xe was

138.12 MHz. Samples were observed using a Bruker 5 mm PABBO NMR probe. ^{129}Xe spectra were processed using standard protocols, and ^{129}Xe NMR spectral calibration was performed as previously reported for cryptophane solutions in $C_2D_2Cl_4$.[2] All air- and moisture-sensitive reactions were performed under inert atmosphere in glassware flamed under vacuum, and using anhydrous solvents. Standard workup procedures involved multiple (~3) extractions with the indicated organic solvent, followed by washing of the combined organic extracts with water or brine, drying over Na_2SO_4 and removal of solvents *in vacuo*. All yields are reported after purification by column chromatography or crystallization.

Materials

Organic reagents and solvents were used as purchased from the following commercial sources: *Sigma-Aldrich*: dimethyl sulfoxide (DMSO, anhydrous, 99.9%), (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (Mosher's acid chloride, 98%, Aldrich); *Fisher:* acetone (HPLC grade), sodium hydroxide, potassium hydroxide, hydrochloric acid, sodium sulfate (anhydrous), sodium chloride, sea sand (washed), potassium carbonate (K_2CO_3, anhydrous), methyl iodide, toluene (HPLC grade), ethyl acetate (EtOAc, HPLC grade), hexanes (HPLC grade), chloroform ($CHCl_3$, HPLC grade), dichloromethane (CH_2Cl_2, HPLC grade), methyl alcohol (MeOH, HPLC grade), ethyl ether (Et_2O, anhydrous); *Acros Organics*: 4-dimethylaminopyridine (DMAP), *N*,*N*-dimethylformamide (DMF, anhydrous, 99.8%), sodium hydride (NaH, 60% dispersion in mineral oil), allyl bromide (99%), benzyl bromide (98%), propargyl bromide (80% solution in toluene), 3,4-dihydroxybenzaldehyde (97%), fluorobenzene (99%), dichloromethane (99.8%, extra dry, over molecular sieves), cesium carbonate (Cs_2CO_3, 99.5%), anhydrous dimethylsulfoxide (DMSO), anhydrous dimethylformamide (DMF), methyl

sulfoxide-d_6, chloroform-*d* ($CDCl_3$), acetone-d_6, 4-hydroxy-3-methoxybenzyl alcohol (99%), 1,2-dibromoethane, sodium borohydride ($NaHB_4$, powder, 98%), scandium(III) trifluoromethanesulfonate ($Sc(OTf)_3$, 95%); methyl alcohol (MeOH, extra dry, over molecular sieves), tetrahydrofuran (THF, extra dry, over molecular sieves), acetonitrile (CH_3CN, anhydrous); *Concord Specialty Gases*: xenon gas (scientific grade). Triethylamine (Et_3N, *Acros*) was distilled from KOH under nitrogen prior to use.

Synthetic Procedures and Analytical Data

Trihydroxy cryptophane (**1**) was obtained in six steps with an overall yield of 9.5%.[2]

Cryptophane (**2**, diastereomeric mixture): An oven-dried flask was charged with trihydroxy cryptophane **1** (0.201 g, 0.236 mmol, 1.0 equiv), DMAP (0.010 g, 0.078 mmol, 0.3 equiv), and triethylamine (2 mL) in DMF (12 mL). Finally, Mosher's acid chloride (0.197 g, 0.778 mmol, 3.3 equiv) was added and the reaction mixture was stirred at 70 ºC for 2 days. The reaction mixture was cooled to rt followed by standard workup procedure using dichloromethane for extraction. The diastereomers were purified and separated by silica gel column chromatography (Et_2O:CH_2Cl_2, 0.5:99.5, *v/v*) to yield 0.12 g (0.081 mmol, yield: 34%) **2a** and of 0.12 g (0.081 mmol, yield: 34%) **2b** as white solids. Typically 20-30% of the trihydroxy cryptophane starting material was recovered from the chromatography column.

*Diastereomer **2a-(S)-(-)***: mp >130 °C dec; TLC (silica gel, Et_2O: CH_2Cl_2, 1:99, v/v): $R_{f(\mathbf{2a})}$ = 0.63; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.73-7.55 (m, 15H), 6.78 (s, 3H), 6.67 (s, 3H), 6.65 (s, 3H), 6.59 (s, 3H), 4.67 (d, *J* = 13.8 Hz, 3H), 4.54 (d, *J* = 13.7 Hz, 3H), 4.37-3.91 (m, 12H), 3.82 (s, 9H), 3.50 (d, *J* = 12.6 Hz, 3H), 3.43 (s, 9H), 3.37 (d, *J* = 13.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm): 164.6, 149.0, 148.9, 144.6, 138.8, 138.2, 133.2, 132.3, 132.0, 131.2, 130.0, 128.5, 127.6,

122.6, 122.4, 117.0, 114.9, 68.8, 68.5, 56.0, 55.4, 36.2, 36.0; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{81}H_{69}F_9O_{18}Na$, 1523.4238; found, 1523.4221.

Diastereomer ***2b-(S)-(+)***: mp >220 °C dec; TLC (silica gel, Et_2O: CH_2Cl_2, 1:99, v/v): $R_{f(\mathbf{2b})}$ = 0.60; ^1H NMR ($CDCl_3$) δ (ppm): 7.75-7.55 (m, 15H), 6.87 (s, 3H), 6.76 (s, 3H), 6.55 (s, 3H), 6.44 (s, 3H), 4.68 (d, *J* = 13.9 Hz, 3H), 4.51 (d, *J* = 13.7 Hz, 3H), 4.26-3.88 (m, 12H), 3.77 (s, 9H), 3.53 (d, *J* = 13.9 Hz, 3H), 3.48 (s, 9H), 3.31 (d, *J* = 13.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm): 164.5, 149.8, 149.5, 146.0, 139.1, 139.0, 133.9, 133.2, 132.2, 131.3, 130.0, 128.7, 128.1, 123.3, 122.4, 119.2, 114.7, 69.3, 69.2, 55.9, 36.6, 36.3; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{81}H_{69}F_9O_{18}Na$, 1523.4238; found, 1523.4202.

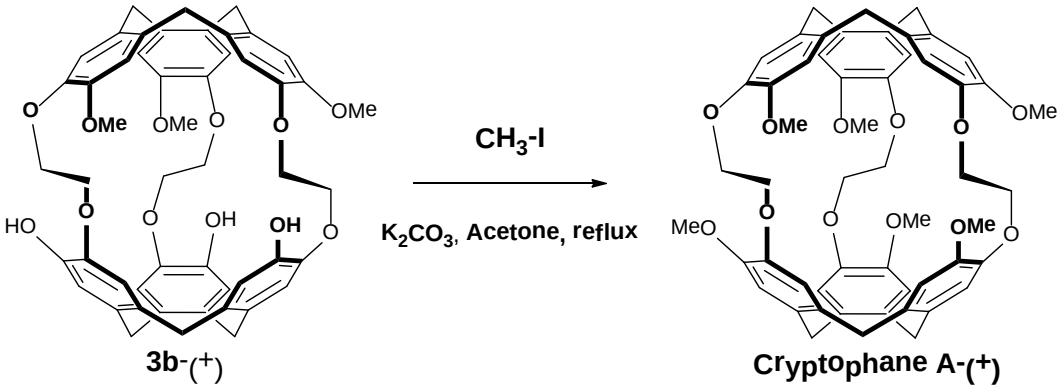
Trihydroxy cryptophane ***3a-(-)***: A solution of 2 M KOH (4 mL) was added to the solution of cryptophane ***2a-(S)-(-)*** (0.051 g, 0.034 mmol) in THF (6 mL). The solution was stirred overnight at 70 °C. THF was removed under vacuum. Water was then added and the resulting solution was acidified with concentrated HCl and extracted with CH_2Cl_2. The solution was washed with water and the organic layer was dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude mixture was purified by silica gel column chromatography (MeOH: CH_2Cl_2, 1:99, v/v) to yield 0.022 g (0.026 mmol, yield: 77%). TLC (silica gel, MeOH/CH_2Cl_2, 5:95, *v/v*): $R_{f(\mathbf{3a})}$ = 0.33; mp >200 °C dec; ^1H NMR and ^{13}C NMR spectra for **3a** are identical to the spectra of the racemic (±) trihydroxy cryptophane previously reported in our lab;[2,3] HRMS (m/z): $[M+Na]^+$ calcd for $C_{51}H_{48}O_{12}Na$, 875.3043; found, 875.3047.

Trihydroxy cryptophane ***3b-(+)***: Following the procedure for the synthesis of **3a**, compound ***2b-(S)-(+)*** (0.049 g, 0.033 mmol) in the presence of 2 M KOH (4 mL) in THF (6 mL) afforded 0.023 g (0.027 mmol, 81% yield) of **3b** as a white solid. TLC (silica gel, MeOH/CH_2Cl_2, 5:95, *v/v*): $R_{f(\mathbf{3b})}$ = 0.33. mp >200 °C dec; ^1H NMR and ^{13}C NMR spectra for **3b** are identical to the

spectra of **3a** and the racemic (±) trihydroxy cryptophane previously reported in our lab,[2,3] for confirmation, HRMS (m/z): $[M+Na]^+$ calcd for $C_{51}H_{48}O_{12}Na$ 875.3043; found, 875.3041.

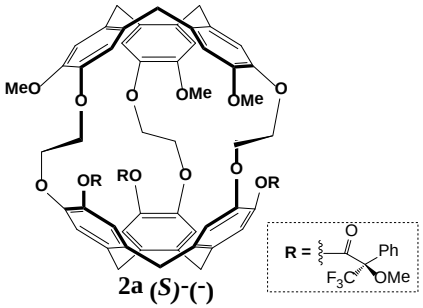
*Tripropargyl cryptophane **4a-(-)***: Compound **3a** (0.041 g, 0.048 mmol, 1 equiv) and K_2CO_3 (0.033 g, 0.24 mmol, 5 equiv) were added into dry acetone (10 mL) under nitrogen. The mixture was stirred at rt for 30 min. The reaction mixture was cooled to 0°C and propargyl bromide (0.05 mL, 0.48 mmol, 10 equiv) was then added dropwise followed by stirring for 30 min at rt. Finally, the reaction mixture was refluxed for 2 days with stirring. The solvent was removed *in vacuo* and the crude mixture was purified by silica gel column chromatography (CH_2Cl_2→Acetone: CH_2Cl_2 5:95, v/v) to yield 0.024 g (0.025 mmol, 52% yield) of **4a** as a white powder. mp >200 °C dec; TLC (silica gel, acetone: CH_2Cl_2, 1:9, *v/v*): $R_{f(\mathbf{4a})}$ = 0.73; ^{1}H NMR and ^{13}C NMR spectra for **4a** are identical to the spectra of the racemic (±) tripropargyl cryptophane previously reported in our lab;[2] HRMS (m/z): $[M+Na]^+$ calcd for $C_{60}H_{54}O_{12}Na$, 989.3513; found, 989.3514.

*Tripropargyl cryptophane **4b-(+)***: Following the procedure for the synthesis of **4a**, compound **3b** (0.045 g, 0.053 mmol, 1 equiv) in the presence of K_2CO_3 (0.037 g, 0.27 mmol, 5 equiv) and propargyl bromide (0.06 mL, 0.53 mmol, 10 equiv) in dry acetone (10 mL) afforded 0.028 g (0.029 mmol, 55% yield) of **4b** as a white solid, mp >200 °C dec; TLC (silica gel, acetone: CH_2Cl_2, 1:9, v/v): $R_{f(\mathbf{4b})}$ = 0.73. ^{1}H NMR and ^{13}C NMR spectra for **4b** are identical to the spectra of **4a** and the racemic (±) tripropargyl cryptophane previously reported in our lab;[2] HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{60}H_{54}O_{12}Na$, 989.3513; found, 989.3533.



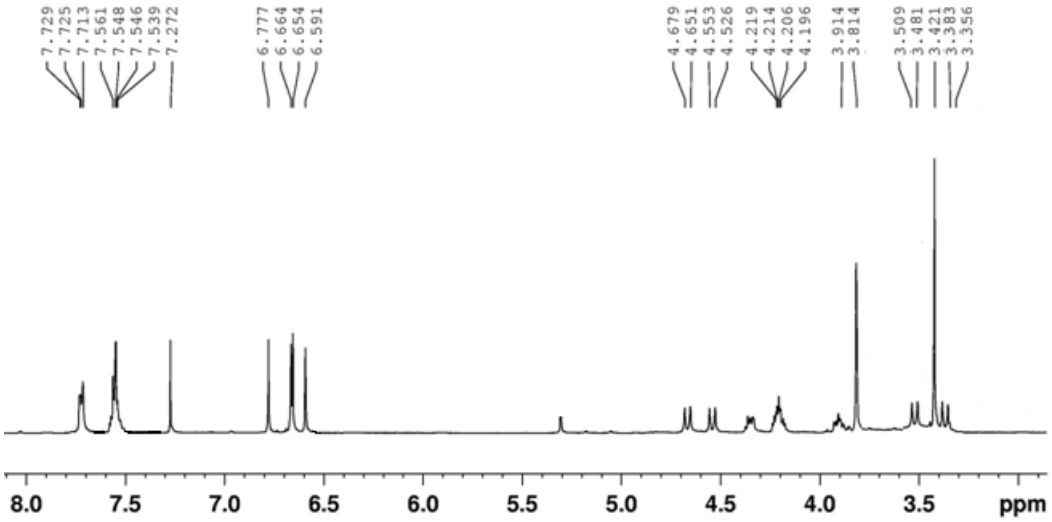
*Cryptophane-A-**(+)*:** An excess of methyl iodide (0.035 g, 0.25 mmol, 10 equiv) was added to **3b-(+)** (0.021 g, 0.025 mmol, 1 equiv) and K_2CO_3 (0.017 g, 0.13 mmol, 5 equiv) in dry acetone (5 mL) under nitrogen. The reaction mixture was refluxed for 2 days with stirring. The solvent was removed *in vacuo* and the crude was purified by silica gel column chromatography (CH_2Cl_2→Acetone:CH_2Cl_2 5:95, v/v) to yield 0.018 g (0.021 mmol, 85% yield) of **5** as a white powder. TLC (silica gel, acetone:CH_2Cl_2, 1:9, v/v): $R_{f(5)}$ = 0.82; ^{1}H NMR ($CDCl_3$) δ (ppm): 6.77 (s, 6H), 6.68 (s, 6H), 4.61 (d, *J* = 13. Hz, 6H), 4.17 (m, 12H), 3.81 (s, 9H), 3.42 (d, *J* = 13.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm): 149.9, 146.9, 134.4, 131.8, 121.0, 113.9, 69.6, 55.9, 36.4. HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{54}H_{54}O_{12}Na$, 917.3513; found, 917.3517.

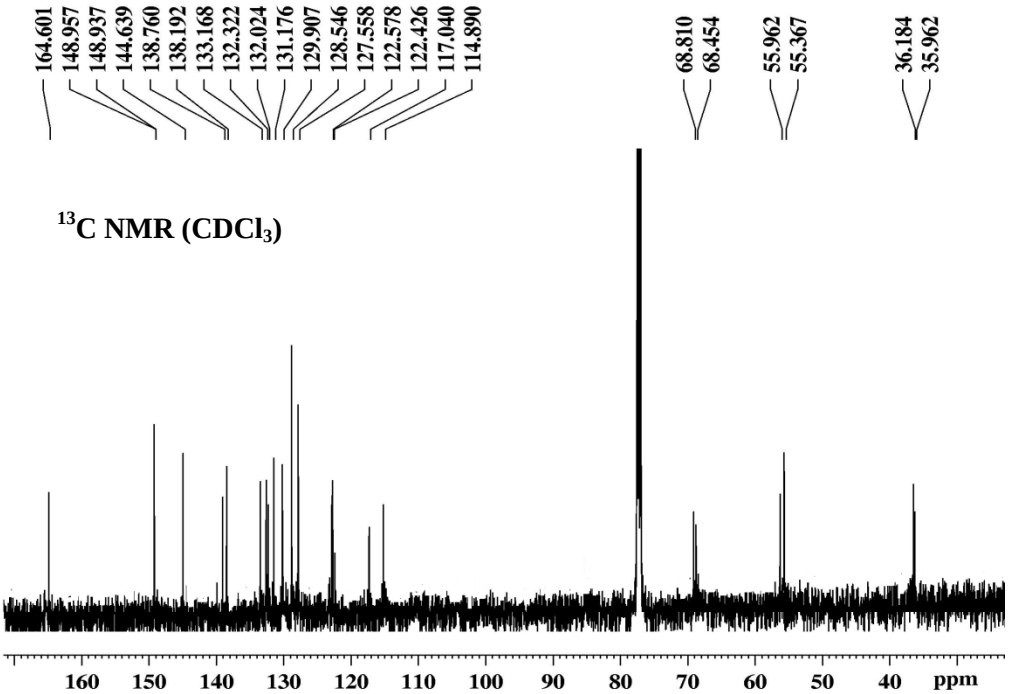
NMR Data (^{1}H and ^{13}C NMR Spectra):



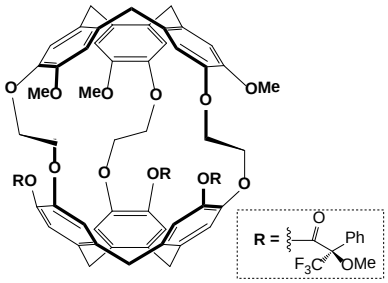
2a (*S*)-(-)

^{1}H NMR ($CDCl_3$)



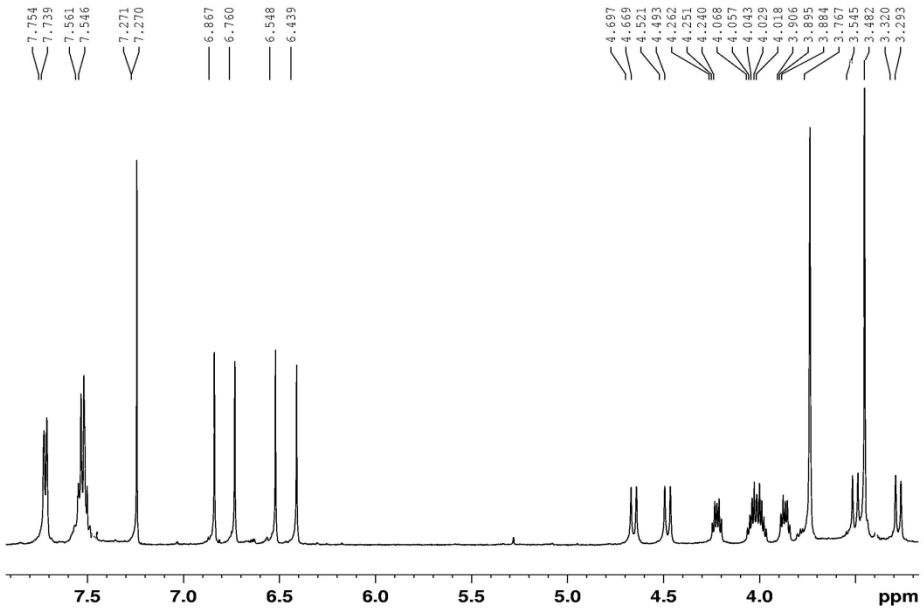


^{13}C NMR ($CDCl_3$)

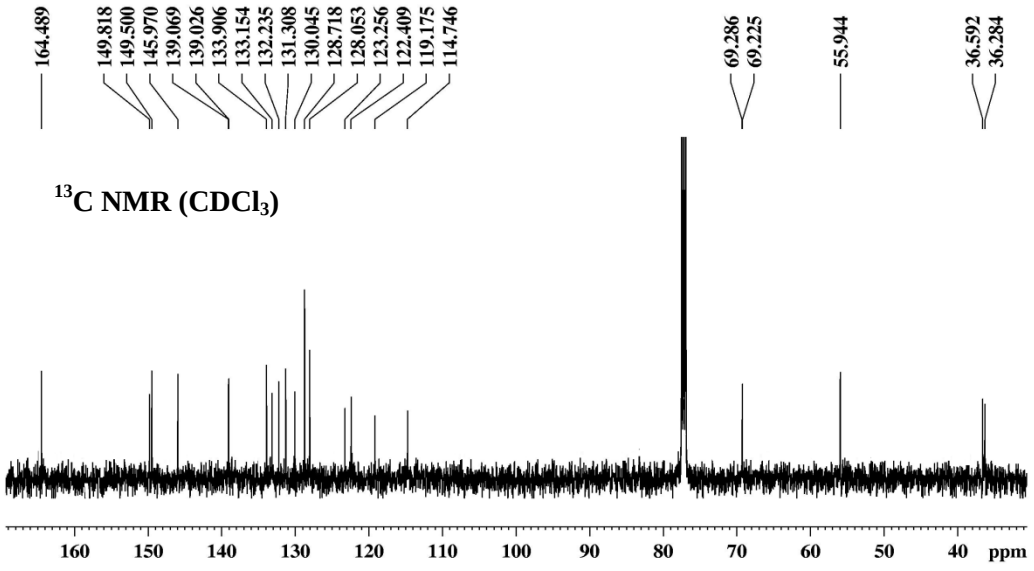


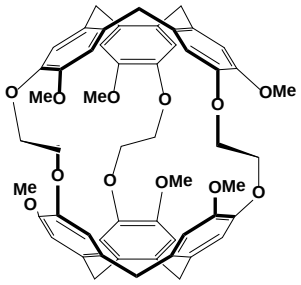
2b (*S*)-(+)

^{1}H NMR ($CDCl_3$)



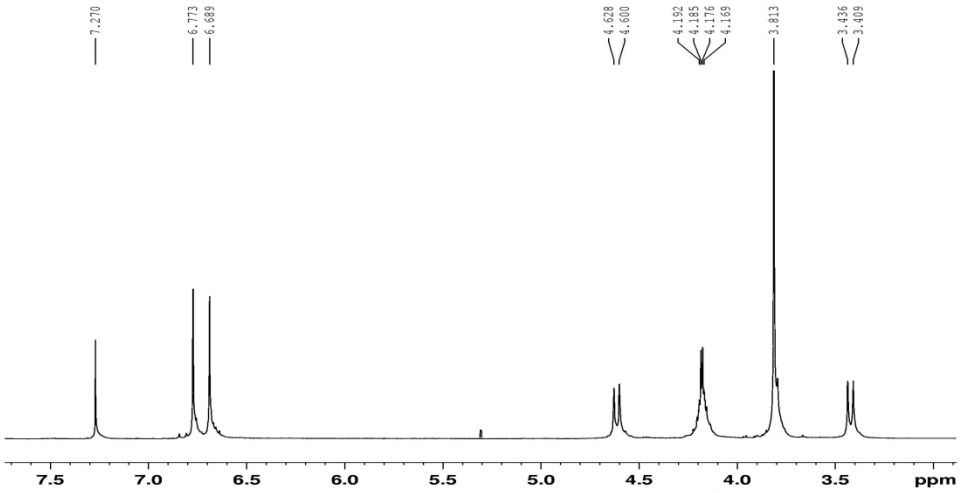
^{13}C NMR ($CDCl_3$)



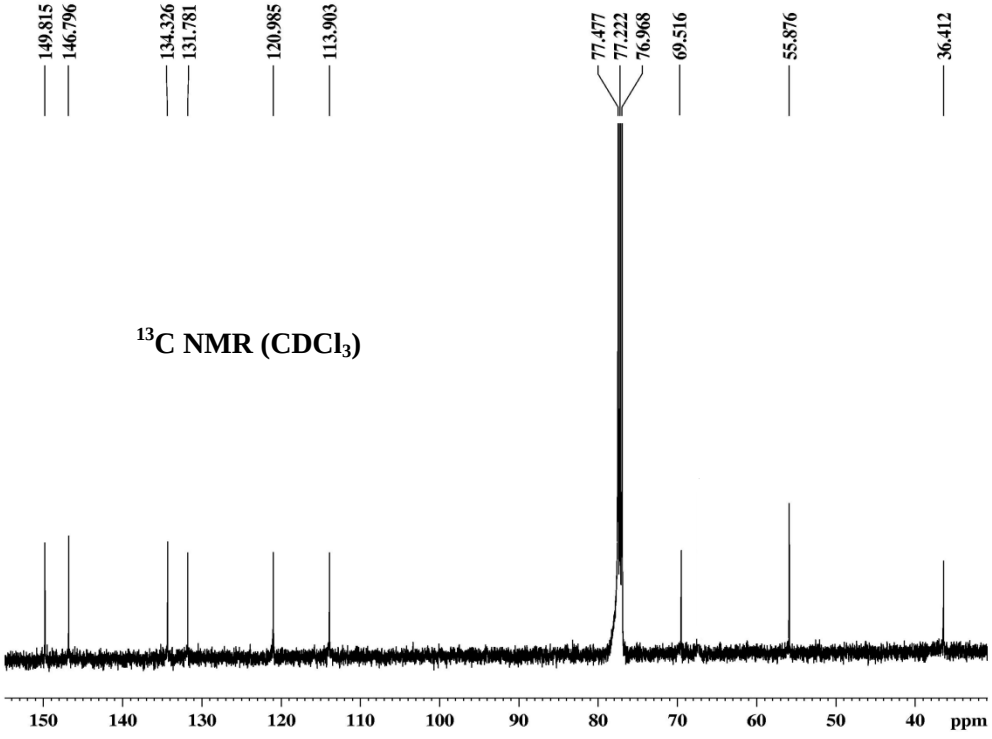


Cryptophane-A-(+)

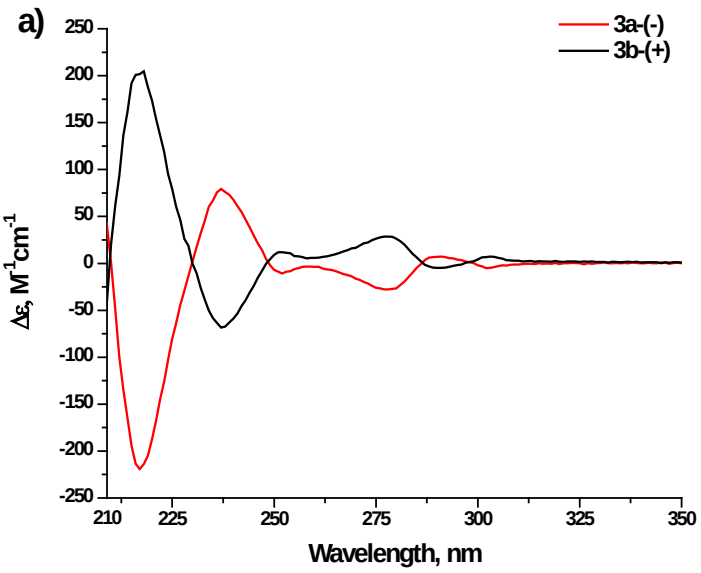
^{1}H NMR ($CDCl_3$)

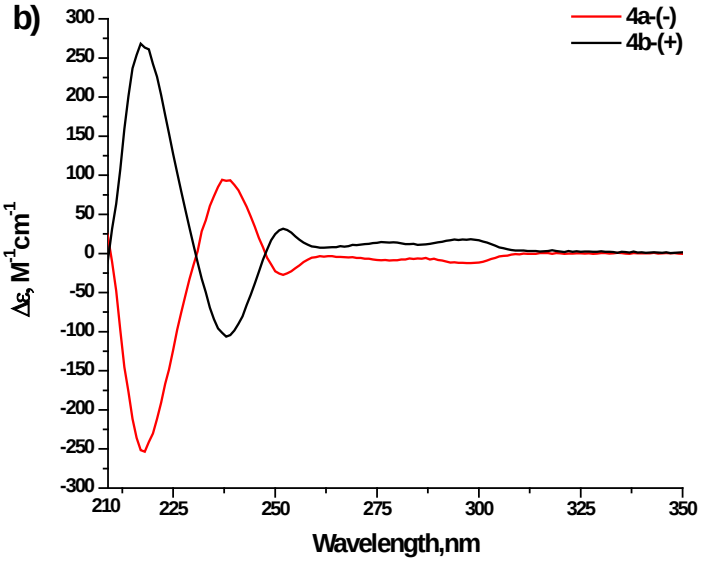


^{13}C NMR ($CDCl_3$)



Electronic Circular Dichroism (ECD) and UV-Vis Spectra:





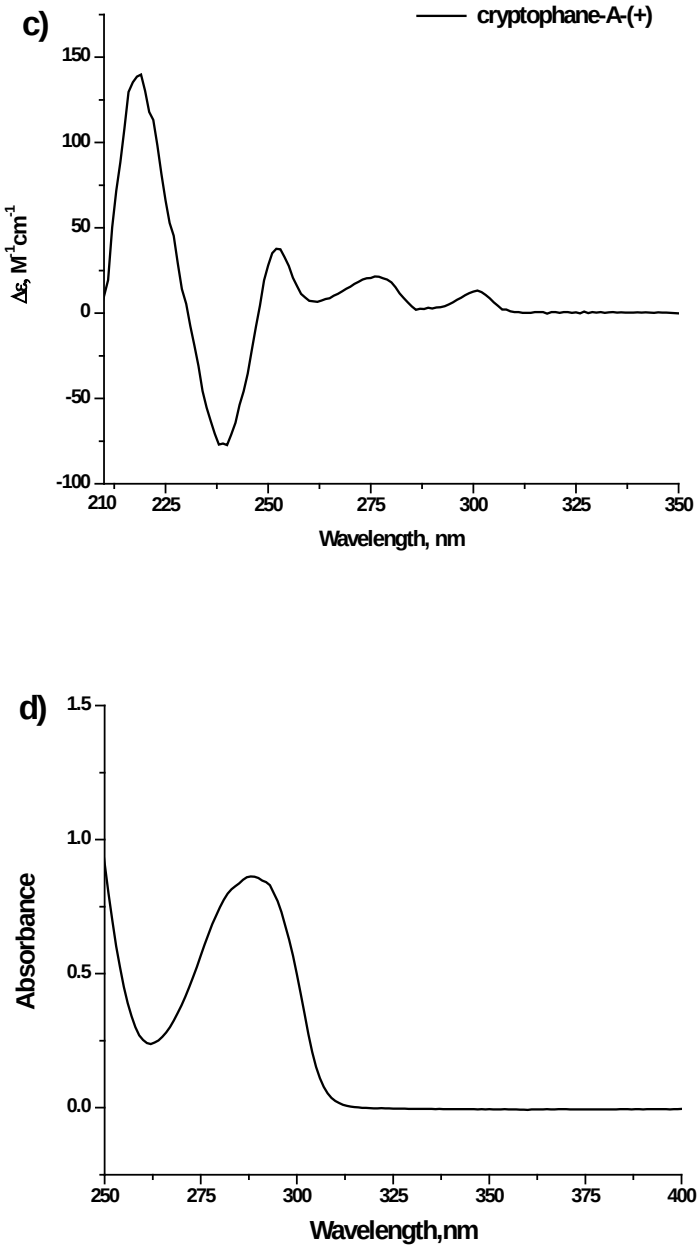
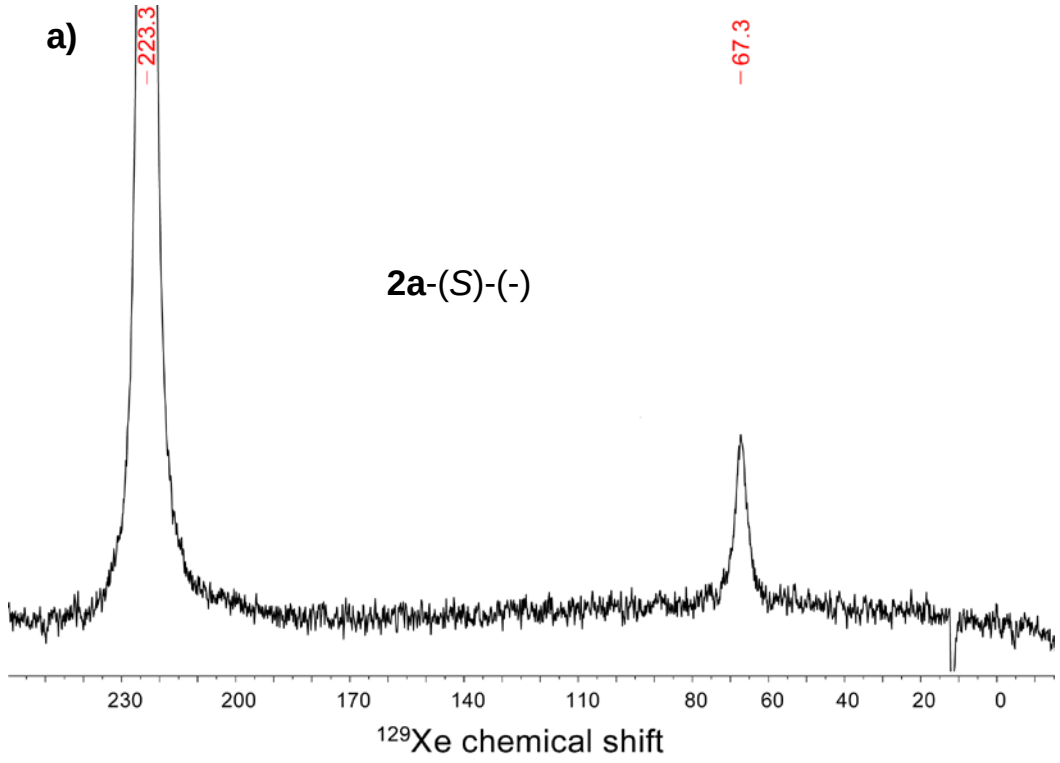


Figure S1. ECD spectra of (**a**) enantiomers **3a-(-)** and **3b-(+)**, (**b**) enantiomers **4a-(-)** and **4b-(+)**, and (**c**) (+)-cryptophane-A in 1,4-dioxane. $\Delta\varepsilon_{282}$ is 10,000 ± 1000 $M^{-1}cm^{-1}$ for all reported cryptophanes (**2a**, **2b**, **3a**, **3b**, **4a**, and **4b**) in 1,4-dioxane. (d) UV-Vis spectrum of tri-propargyl cryptophane-A (compound **4**, 7×10^{-5} M solution in 1,4-dioxane).

^{129}Xe NMR Spectra:



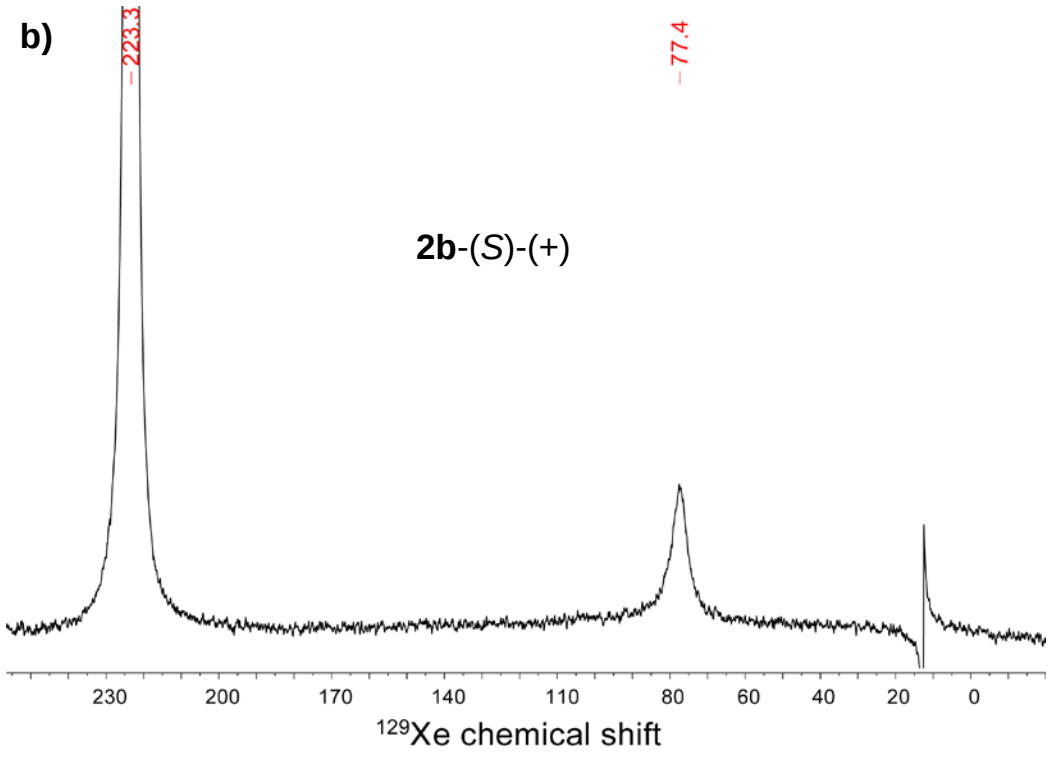


Figure S2. ^{129}Xe NMR spectra of (**a**) diastereomer **2a**, and (**b**) diastereomer **2b**. Both diastereomers (~ 10 mM) were dissolved in $C_2D_2Cl_4$ and spectra were recorded at room temperature. Spectra are not temperature corrected, thus absolute and relative chemical shift values differ somewhat from spectrum of the mixture of diastereomers shown in the main text. Apart from the Xe@cryptophane peaks described in the main text, the peak of dissolved Xe in solvent (223.3 ppm) and the mirror image of this peak (around 10 ppm) are also present. Spectra are scaled to optimize the view of the cryptophane peaks.

References:

(1) Chambers, J. M.; Hill, P. A.; Aaron, J. A.; Han, Z.; Christianson, D. W.; Kuzma, N. N.; Dmochowski, I. J. *J. Am. Chem. Soc.* **2008**, *131*, 563.

(2) Taratula, O.; Hill, P. A.; Bai, Y. B.; Khan, N. S.; Dmochowski, I. J. *Org. Lett.* **2011**, *13*, 1414.

(3) Hill, P. A.; Wei, Q.; Troxler, T.; Dmochowski, I. J. *J. Am. Chem. Soc.* **2009**, *131*, 3069.