



Chiroptical study of cryptophanes subjected to self-encapsulation

Orsola Baydoun, Thierry Buffeteau, Nicolas Daugey, Marion Jean, Nicolas Vanthuyne, Laure-lise Chapellet, Nicolas de Rycke, Thierry Brotin

► To cite this version:

Orsola Baydoun, Thierry Buffeteau, Nicolas Daugey, Marion Jean, Nicolas Vanthuyne, et al.. Chiroptical study of cryptophanes subjected to self-encapsulation. *Chirality*, 2019, 10.1002/chir.23079 . hal-02141856

HAL Id: hal-02141856

<https://hal.science/hal-02141856>

Submitted on 20 Mar 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Chiroptical Study of Cryptophanes Subjected to Self-Encapsulation

Orsola Baydoun,[†] Thierry Buffeteau^{,‡} Nicolas Daugey,[‡] Marion Jean,[§] Nicolas Vanthuyne,[§]*

Laure-Lise Chapellet,[†] Nicolas De Rycke[†] and Thierry Brotin,^{,‡}*

[†] Lyon 1 University, Ecole Normale Supérieure de Lyon, CNRS UMR 5182, Laboratoire de Chimie, 69364 Lyon, France

[‡] Bordeaux University, Institut des Sciences Moléculaires, CNRS UMR 5255, 33405 Talence, France

[§] Aix-Marseille University, CNRS, Centrale Marseille, iSm2, Marseille, France

e-mail: thierry.buffeteau@u-bordeaux.fr; thierry.brotin@ens-lyon.fr

Table of contents :

Figure S1: Chromatograms (Chiralpak IC, 250 x 4.6 mm, heptane/ethanol/CH₂Cl₂: 50/10/40, 1 mL/min at 25 °C) of the (rac)-**1** before preparative separation on Chiralpak IC (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 50/10/40, 5 mL/min).

Figure S2: Chromatograms (Chiralpak IC, 250 x 4.6 mm, heptane/ethanol/CH₂Cl₂: 50/10/40, 1 mL/min at 25 °C) of the collected [CD(-)₂₅₄]-**1** and [CD(+)₂₅₄]-**1** after preparative separation on Chiralpak IC (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 50/10/40, 5 mL/min). Detection performed by UV-Vis spectroscopy at 230 nm (black chromatograms) and CD spectroscopy at 254 nm (red chromatograms).

Figure S3: Experimental procedure for the synthesis of cryptophane **2**.

Figure S4: Experimental procedure for the synthesis of cryptophane **3**.

Figure S5: Chromatograms ((S,S)-Whelk-O₁, 250 x 4.6 mm, heptane/ethanol/CH₂Cl₂: 20/40/40, 1 mL/min at 25 °C) of the (rac)-**2** before preparative separation on (S,S)-Whelk-O₁ (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 20/40/40, 5 mL/min).

Figure S6: Chromatograms ((S,S)-Whelk-O₁, 250 x 4.6 mm, heptane/ethanol/CH₂Cl₂: 20/40/40, 1 mL/min at 25 °C) of the collected [CD(-)₂₅₄]-**2** and [CD(+)₂₅₄]-**2** after preparative separation on (S,S)-Whelk-O₁ (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 20/40/40, 5 mL/min). Detection performed by UV-Vis spectroscopy at 230 nm (black chromatograms) and CD spectroscopy at 254 nm (red chromatograms).

Figure S7: Chromatograms ((S,S)-Whelk-O₁, 250 x 4.6 mm, ethanol/CH₂Cl₂: 50/50, 1 mL/min at 25 °C) of the (rac)-**3** before preparative separation on (S,S)-Whelk-O₁ (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 35/65, 5 mL/min).

Figure S8: Chromatograms ((S,S)-Whelk-O₁, 250 x 4.6 mm, ethanol/CH₂Cl₂: 50/50, 1 mL/min at 25 °C) of the collected [CD(-)₂₅₄]-**3** and [CD(+)₂₅₄]-**3** after preparative separation on (S,S)-Whelk-O₁ (250 x 10 mm, ethanol/CH₂Cl₂: 50/50, 5 mL/min). Detection performed by UV-Vis spectroscopy at 230 nm (black chromatograms) and CD spectroscopy at 254 nm (red chromatograms).

Figure S9: ¹H NMR spectrum (300 MHz) of (rac)-**1** recorded in CD₂Cl₂ at 25 °C. The letters A,B,C,D,E show protons signals related to the imploded form.

Figure S10: ¹H NMR spectrum (300 MHz) of (rac)-**1** recorded in CDCl₃ at 25 °C. The letters A,B,C,D show protons signals related to the imploded form.

Figure S11: ¹H NMR spectrum (300 MHz) of (rac)-**1** recorded in DMSO-d₆ at 25 °C.

Figure S12: ¹H NMR spectrum (300 MHz) of (rac)-**1** recorded in 1,1,2,2-tetrachloroethane-d₂ at 25 °C.

Figure S13: ¹H NMR spectrum (300 MHz) of (rac)-**2** recorded in CD₂Cl₂ at 25 °C.

Figure S14: ^1H NMR spectrum (300 MHz) of (rac)-**2** recorded in CDCl_3 at 25 °C.

Figure S15: ^1H NMR spectrum (300 MHz) of (rac)-**2** recorded in 1,1,2,2-tetrachloroethane- d_2 at 25 °C.

Figure S16: ^1H NMR spectrum (300 MHz) of (rac)-**2** recorded in benzene- d_6 at 25 °C.

Figure S17: Specific Optical Rotation (SOR) values measured for $[\text{CD}(+)]_{254}\text{-1}$ and $[\text{CD}(-)]_{254}\text{-1}$ in CH_2Cl_2 (black), CHCl_3 (orange), DMSO (blue) and $\text{C}_2\text{H}_2\text{Cl}_4$ (red) at 25 °C. Plot of the SOR (10^{-1} deg $\text{cm}^2 \text{g}^{-1}$) values versus λ (nm) for the $[\text{CD}(+)]_{254}\text{-1}$ enantiomer.

Figure S18: Specific Optical Rotation (SOR) values measured for $[\text{CD}(+)]_{254}\text{-2}$ and $[\text{CD}(-)]_{254}\text{-2}$ in CH_2Cl_2 (black), CHCl_3 (orange), DMSO (blue) and $\text{C}_2\text{H}_2\text{Cl}_4$ (red) at 25 °C. Plot of the SOR (10^{-1} deg $\text{cm}^2 \text{g}^{-1}$) values versus λ (nm) for the $[\text{CD}(+)]_{254}\text{-2}$ enantiomer.

Figure S19: Specific Optical Rotation (SOR) values measured for $[\text{CD}(+)]_{254}\text{-3}$ and $[\text{CD}(-)]_{254}\text{-3}$ in CH_2Cl_2 (black), CHCl_3 (orange), DMSO (blue) and $\text{C}_2\text{H}_2\text{Cl}_4$ (red) at 25 °C. Plot of the SOR (10^{-1} deg $\text{cm}^2 \text{g}^{-1}$) values versus λ (nm) for the $[\text{CD}(+)]_{254}\text{-3}$ enantiomer.

Figure S20: ECD spectra of $[\text{CD}(+)]_{254}\text{-1}$ (black spectra) and $[\text{CD}(-)]_{254}\text{-1}$ (red spectra) recorded in CH_2Cl_2 , CHCl_3 , THF, CH_3CN , DMSO and $\text{C}_2\text{H}_2\text{Cl}_4$ at 20 °C. ($c = 10^{-4} - 10^{-5}$ M). UV-visible spectrum of **1** recorded in THF at 25 °C ($c = 1.12 \cdot 10^{-5}$ M).

Figure S21: ECD spectra of $[\text{CD}(+)]_{254}\text{-2}$ (black spectra) and $[\text{CD}(-)]_{254}\text{-2}$ (red spectra) recorded in CH_2Cl_2 , CHCl_3 , THF, CH_3CN , DMSO and $\text{C}_2\text{H}_2\text{Cl}_4$ at 20 °C. ($c = 10^{-4} - 10^{-5}$ M). UV-visible spectrum of **2** recorded in THF at 25 °C ($c = 1.02 \cdot 10^{-5}$ M).

Figure S22: ECD spectra of $[\text{CD}(+)]_{254}\text{-3}$ (black spectra) and $[\text{CD}(-)]_{254}\text{-3}$ (red spectra) recorded in CH_2Cl_2 , CHCl_3 , THF, CH_3CN , DMSO and $\text{C}_2\text{H}_2\text{Cl}_4$ at 20 °C. ($c = 10^{-4} - 10^{-5}$ M). UV-visible spectrum of **3** recorded in THF at 25 °C ($c = 0.99 \cdot 10^{-5}$ M).

Figure S23: IR spectra of a) $[\text{CD}(+)]_{254}\text{-1}$, b) $[\text{CD}(+)]_{254}\text{-2}$ and $[\text{CD}(+)]_{254}\text{-3}$ c) in CDCl_3 (black spectra), CD_2Cl_2 (red spectra) and $\text{C}_2\text{D}_2\text{Cl}_4$ (blue spectra) solvents (0.015 mM, 250 μm path length).

Figure S24: VCD spectra of $[\text{CD}(+)]_{254}\text{-1}$ (black spectra) and $[\text{CD}(-)]_{254}\text{-1}$ (red spectra) in a) CDCl_3 , b) CD_2Cl_2 , and c) $\text{C}_2\text{D}_2\text{Cl}_4$ solvents (0.015 mM, 250 μm path length).

Figure S25: VCD spectra of $[\text{CD}(+)]_{254}\text{-2}$ (black spectra) and $[\text{CD}(-)]_{254}\text{-2}$ (red spectra) in a) CDCl_3 , b) CD_2Cl_2 , and c) $\text{C}_2\text{D}_2\text{Cl}_4$ solvents (0.015 mM, 250 μm path length).

Figure S26: VCD spectra of $[\text{CD}(+)]_{254}\text{-3}$ (black spectra) and $[\text{CD}(-)]_{254}\text{-3}$ (red spectra) in a) CD_2Cl_2 and b) $\text{C}_2\text{D}_2\text{Cl}_4$ solvents (0.015 mM, 250 μm path length).

Figure S27: Optimized geometry of **PP-1** enantiomer calculated at the density functional theory (DFT) level using B3LYP functional and 6-31G** basis set with the use of IEFPCM model of solvent (IEFPCM = CH_2Cl_2 and $\text{C}_2\text{H}_2\text{Cl}_4$).

Figure S28: Optimized geometry of **MM-2** enantiomer calculated at the density functional theory (DFT) level using B3LYP functional and 6-31G** basis set with the use of IEFPCM model of solvent (IEFPCM = CH₂Cl₂ and C₂H₂Cl₄).

Figure S29: Comparison of experimental VCD spectrum of [CD(−)₂₅₄]-**2** in C₂D₂Cl₄ solution (15 mM, 250 μm path length) and VCD spectra of **MM-2** calculated at the B3LYP/6-31G** level (IEFPCM = C₂H₂Cl₄) for the *trans* and *gauche-gauche* conformations of the ethylenedioxy and propylenedioxy linkers, respectively, and for the acetate group grafted on the propylenedioxy linker pointing inside (blue spectrum) or outside (red spectrum) the cavity.

Table S1: Specific optical rotation values measured for [CD(+)₂₅₄]-**1** in different solvents at 25 °C.

Table S2: Specific optical rotation values measured for [CD(−)₂₅₄]-**1** in different solvents at 25 °C.

Table S3: Specific optical rotation values measured for [CD(+)₂₅₄]-**2** in different solvents at 25 °C.

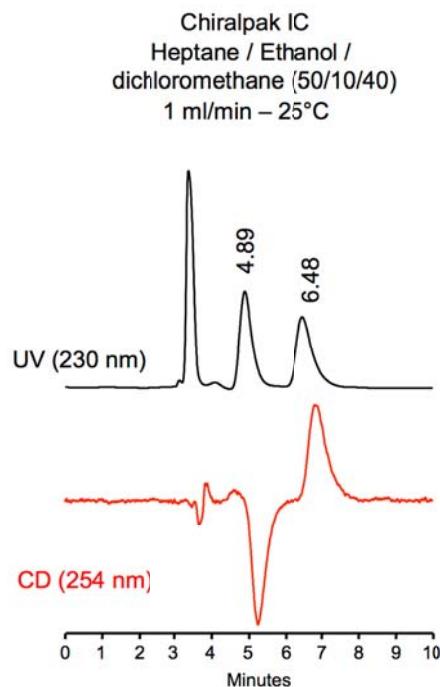
Table S4: Specific optical rotation values measured for [CD(−)₂₅₄]-**2** in different solvents at 25 °C.

Table S5: Specific optical rotation values measured for [CD(+)₂₅₄]-**3** in different solvents at 25 °C.

Table S6: Specific optical rotation values measured for [CD(−)₂₅₄]-**3** in different solvents at 25 °C.

Table S7: B3LYP/6-31G** frequencies (scaled by 0.968) of the ester νC=O stretching vibration of **MM-2** (IEFPCM = CH₂Cl₂ and C₂D₂Cl₄) for the acetate group pointing inward or outward the cavity.

Analytical separation for compound **1**



Column	Mobile Phase	t_1	k_1	t_2	k_2	α	R_s
Chiraldak IC	heptane/EtOH/CH ₂ Cl ₂ (50/10/40)	4.89 (-)	0.63	6.48 (+)	1.16	1.84	2.23

Figure S1: Chromatograms (Chiraldak IC, 250 x 4.6 mm, heptane/ethanol/CH₂Cl₂: 50/10/40, 1 mL/min at 25 °C) of the (rac)-**1** before preparative separation on Chiraldak IC (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 50/10/40, 5 mL/min).

Semi-preparative separation for compound **1**

Sample preparation: About 460 mg of compound (rac)-**1** are dissolved in 18 mL of dichloromethane. Chromatographic conditions: Chiraldak IC (250 x 10 mm), hexane/ethanol/dichloromethane (5/1/4) as mobile phase, flow-rate = 5 ml/min, UV detection at 230 nm. Injections (stacked): 180 times 100 µL, every 5 minutes.

The first eluted enantiomer is collected between 4.2 and 5.2 minutes and the second one between 6 and 7.5 minutes.

First fraction: 180 mg of the first eluted [CD(-)₂₅₄]-**1** with ee > 99.5 % on Jasco CD-1595 circular dichroism detector at 254 nm.

Second fraction: 200 mg of the second eluted [CD(+)₂₅₄]-**1** with ee > 99 % on Jasco CD-1595 circular dichroism detector at 254 nm.

Chiralpak IC
Heptane/Ethanol/Dichloromethane (50/10/40)
1 mL/min - 25°C

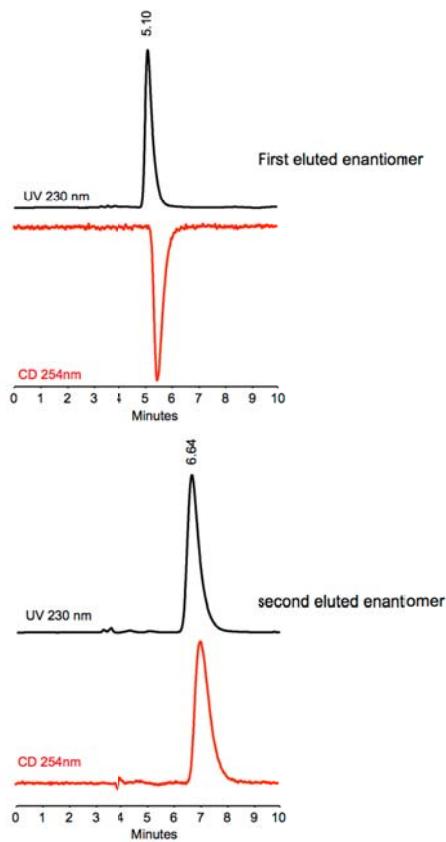
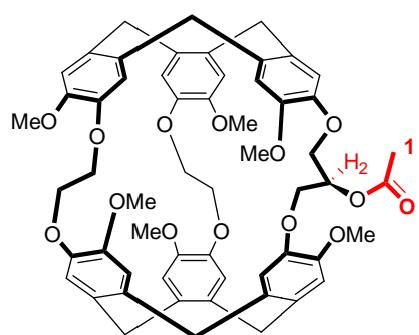
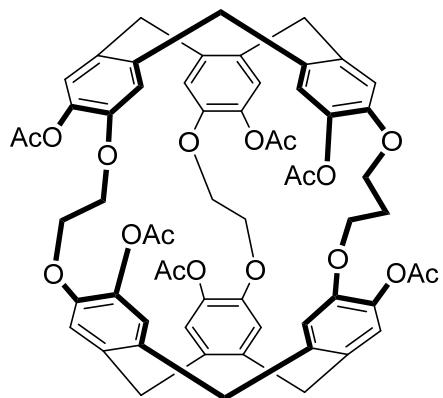


Figure S2: Chromatograms (Chiralpak IC, 250 x 4.6 mm, heptane/ethanol/CH₂Cl₂: 50/10/40, 1 mL/min at 25 °C) of the collected [CD(-)₂₅₄]-**1** and [CD(+)₂₅₄]-**1** after preparative separation on Chiralpak IC (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 50/10/40, 5 mL/min). Detection performed by UV-Vis spectroscopy at 230 nm (black chromatograms) and CD spectroscopy at 254 nm (red chromatograms).



Synthesis of cryptophane 2: Acetic anhydride (0.7 mL, 7.4 mmol, 10 equiv.) was added dropwise at 0 °C to a solution of cryptophane-223(OMe)₆OH (0.7 g, 0.75 mmol) in freshly distilled CH₂Cl₂ (23 mL) and pyridine (3.5 mL). The reaction mixture was stirred for 48 hours at room temperature. The solution was then quenched at 0 °C with concentrated NaHCO₃ (10 ml) for 10 minutes and then poured in 20 mL of H₂O. The aqueous layer was extracted 5 times with CH₂Cl₂ and then dried over Na₂SO₄. After filtration the solvent was evaporated under reduced pressure. The crude product was subjected to column chromatography on silica gel (CH₂Cl₂/acetone: 85/15) to give rise to compound **2** as a white product (0.52 g, 71%). ¹H NMR (300 MHz, CDCl₃, 25 °C) δ ppm: 6.63-6.79 (12 s, 12 H), 4.58-4.62 (m, 6H), 4.02-4.2 (m, 11H), 3.93 (m, 1 H), 3.73- 3.8 (6s, 18 H), 3.47 (m, 1H), 3.36-3.41 (m, 6 H), 2.17 (s, 3H). ¹³C NMR: (75.5 MHz, CDCl₃, 25 °C) δ ppm: 170.6, 149.6 (2C), 149.55, 149.4, 148.8, 148.1, 146.8, 146.7 (2 C), 146.6, 146.5 (2 C), 134.1, 134.1, 133.8, 133.8, 133.3, 132.8, 132.1, 131.9, 131.5, 131.4, 131.35, 131.3, 120.3, 120.2 (3 C), 117.2, 115.1, 114.2 (2 C), 113.9, 113.7, 113.35, 113.2, 70.8, 69.6, 69.5, 69.1, 68.9 (2 C), 66.6, 56.3, 56.3, 55.7, 55.65(2 C), 55.6, 36.5, 36.4; 36.2 (4 C), 21.2. HRMS(ESI-TOF) *m/z* [M + Na]⁺ calcd for C₅₇H₅₈O₁₄Na 989.3724, found 989.3719.

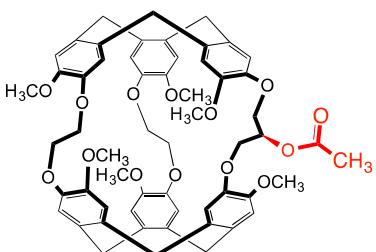
Figure S3: Experimental procedure for the synthesis of cryptophane **2**.



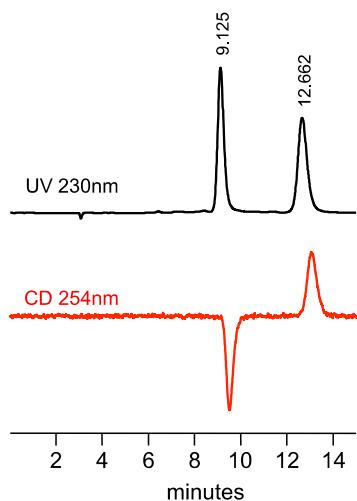
Synthesis of cryptophane 3: Acetic anhydride (2.2 mL, 41 mmol) was added dropwise at 0 °C to a solution of cryptophane223(OH)₆ (0.35g, 0.42 mmol) in Pyridine (5 mL). The reaction was stirred at room temperature for 16 hours under an argon atmosphere. Then, the reaction was quenched with a solution of sodium bicarbonate at 0 °C. The solution was then extracted 5 times with CH₂Cl₂. The combined organic layers were dried over sodium sulfate. A filtration, followed by evaporation of the solvents under reduced pressure, gives rise to compound **3** as a white product. The solid was then washed on a frit with an Et₂O/CH₂Cl₂: 75/25 mixture to give compound **3** as a clean white solid (0.31g, 71 %). ¹H NMR (300 MHz, CDCl₃, 25 °C) δ ppm: 6.94 (s, 2 H), 6.91(2 H), 6.89 (2 H), 6.87 (2 H), 6.86(2 H), 6.62 (2 H), 4.65-4.58 (m, 6 H), 4.28-4.286 (2 H, m), 4.16-4.15 (m, 2 H), 4.04 - 3.8 (m, 8 H), 3.5-3.4 (m, 6H), 2.31 (s, 6 H), 2.29 (s, 6 H), 2.25 (s, 6 H), 2.09 (m, 2 H). ¹³C NMR (75.5 MHz, CDCl₃, 25 °C) δ ppm: 168.5 (4 C), 168.3 (2 C), 149.3 (2 C), 149.25 (2 C), 149.0 (2 C), 140.5 (2 C), 140.3 (2 C), 138.7 (2 C), 138.6 (2 C), 137.8 (2 C), 136.7 (2 C), 133.6 (2 C), 133.4 (2 C), 131.2 (2 C), 124.4 (2 C), 124.0 (2 C), 123.3 (2 C), 120.9 (2 C), 120.7 (2 C), 113.6 (2 C), 69.8 (2 C), 69.1 (2 C), 63.7 (2 C), 36.4 (2 C), 36.1 (4 C), 20.7 (4 C), 20.6 (2 C). HRMS(ESI-TOF) *m/z* [M + Na]⁺ calcd for C₆₁H₅₆O₁₈Na 1099.3364, found 1099.3359.

Figure S4: Experimental procedure for the synthesis of cryptophane **3**.

Analytical separation for compound **2**



(*S,S*)-Whelk-O₁
Heptane/ethanol/CH₂Cl₂
(20/40/40)
1 ml/min – 25°C



Column	Mobile Phase	<i>t</i> ₁	<i>k</i> ₁	<i>t</i> ₂	<i>k</i> ₂	α	<i>R</i> _s
(<i>S,S</i>)-Whelk-O ₁	heptane/EtOH/CH ₂ Cl ₂ 20/40/40	9.13 (-)	2.10	12.67 (+)	3.29	1.57	5.72

Figure S5: Chromatograms ((*S,S*)-Whelk-O₁, 250 x 4.6 mm, heptane/ethanol/CH₂Cl₂: 20/40/40, 1 mL/min at 25 °C) of the (*rac*)-**2** before preparative separation on (*S,S*)-Whelk-O₁ (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 20/40/40, 5 mL/min).

Semi-preparative separation for compound **2**

Sample preparation: About 580 mg of (rac)-**2** are dissolved in 6 mL of dichloromethane. Chromatographic conditions: (S,S)-Whelk-O1 (250 x 10 mm), heptane/ethanol/dichloromethane (20/40/40) as mobile phase, flow-rate = 5 mL/min, UV detection at 230 nm. Injections (stacked): 20 times 300 μ L, every 13.8 minutes.

First fraction: 255 mg of the first eluted [CD(-)₂₅₄]-**2** with ee > 99.5% on Jasco CD-1595 circular dichroism detector at 254 nm.

Second fraction: 240 mg of the second eluted [CD(+)₂₅₄]-**2** with ee > 99.5% on Jasco CD-1595 circular dichroism detector at 254 nm.

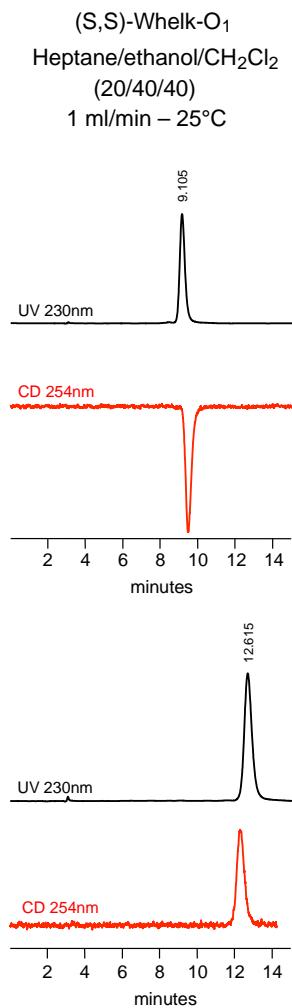
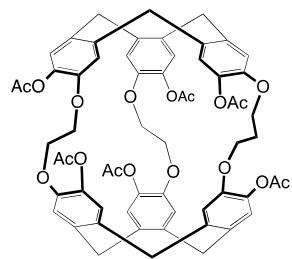
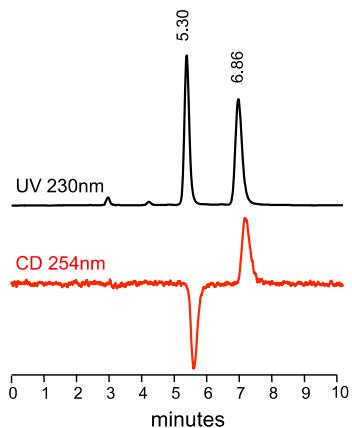


Figure S6: Chromatograms ((S,S)-Whelk-O₁, 250 x 4.6 mm, heptane/ethanol/CH₂Cl₂: 20/40/40, 1 mL/min at 25 °C) of the collected [CD(-)₂₅₄]-**2** and [CD(+)₂₅₄]-**2** after preparative separation on (S,S)-Whelk-O₁ (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 20/40/40, 5 mL/min). Detection performed by UV-Vis spectroscopy at 230 nm (black chromatograms) and CD spectroscopy at 254 nm (red chromatograms).

Analytical separation for compound **3**



(S,S)-Whelk-O1
Ethanol/CH₂Cl₂
(50/50)
1 ml/min – 25°C



Column	Mobile Phase	t_1	k_1	t_2	k_2	α	R_s
(S,S)-Whelk-O1	ethanol/CH ₂ Cl ₂ 50/50	5.30 (-)	0.80	6.86 (+)	1.32	1.67	4.81

Figure S7: Chromatograms ((S,S)-Whelk-O₁, 250 x 4.6 mm, ethanol/CH₂Cl₂: 50/50, 1 mL/min at 25 °C) of the (rac)-**3** before preparative separation on (S,S)-Whelk-O₁ (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 35/65, 5 mL/min).

Semi-preparative separation for compound 3

Sample preparation: About 575 mg of compound (rac)-3 are dissolved in 170 mL of a mixture of ethanol/dichloromethane (30/70). Chromatographic conditions: (S,S)-Whelk-O₁ (250 x 10 mm), ethanol/dichloromethane (35/65) as mobile phase, flow-rate = 5 ml/min, UV detection at 230 nm. Injections (stacked): 340 times 500 µL, every 4.4 minutes.

First fraction: 235 mg of the first eluted [CD(-)₂₅₄]-3 with ee > 99% on Jasco CD-1595 circular dichroism detector at 254 nm.

Second fraction: 200 mg of the second eluted [CD(+)₂₅₄]-3 with ee > 99.5% on Jasco CD-1595 circular dichroism detector at 254 nm.

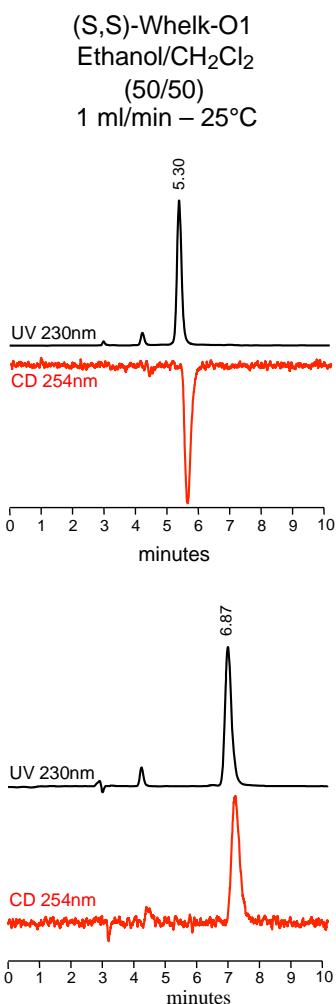


Figure S8: Chromatograms ((S,S)-Whelk-O₁, 250 x 4.6 mm, ethanol/CH₂Cl₂: 50/50, 1 mL/min at 25 °C) of the collected [CD(-)₂₅₄]-3 and [CD(+)₂₅₄]-3 after preparative separation on (S,S)-Whelk-O₁ (250 x 10 mm, ethanol/CH₂Cl₂: 50/50, 5 mL/min). Detection performed by UV-Vis spectroscopy at 230 nm (black chromatograms) and CD spectroscopy at 254 nm (red chromatograms).

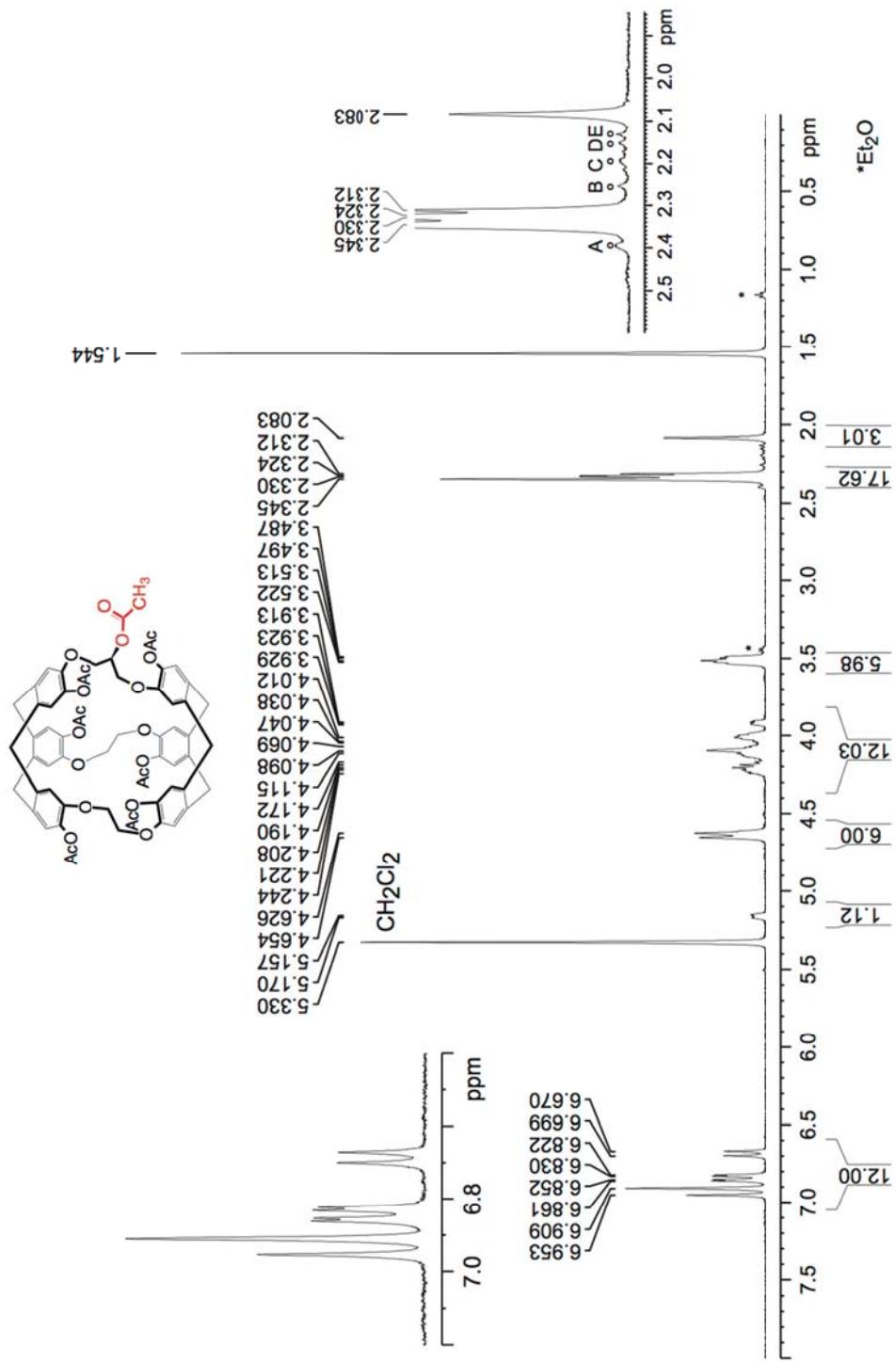


Figure S9: ¹H NMR spectrum (300 MHz) of (rac)-1 recorded in CD₂Cl₂ at 25 °C. The letters A,B,C,D,E show protons signals related to the imploded form.

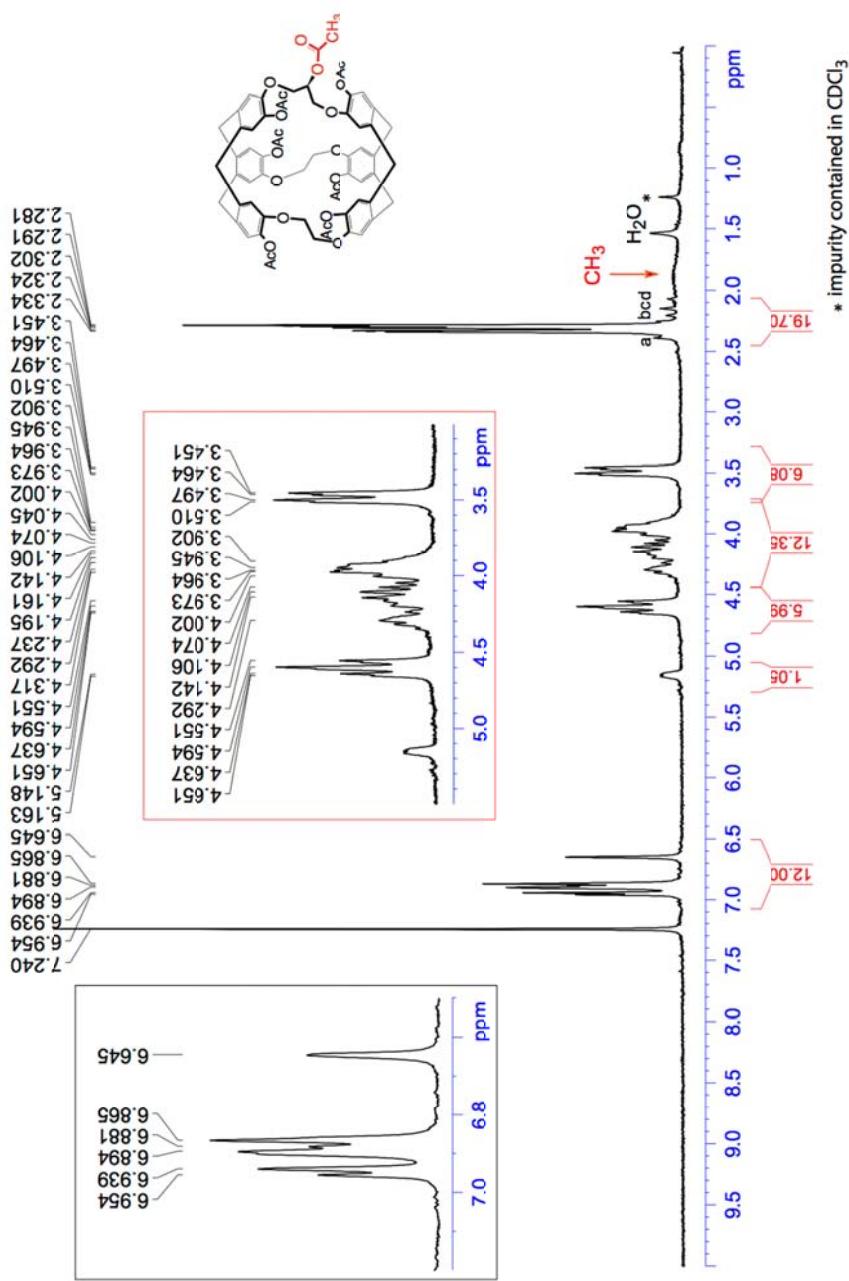


Figure S10: ^1H NMR spectrum (300 MHz) of (rac)-1 recorded in CDCl_3 at 25 °C. The letters A,B,C,D show protons signals related to the imploded form.

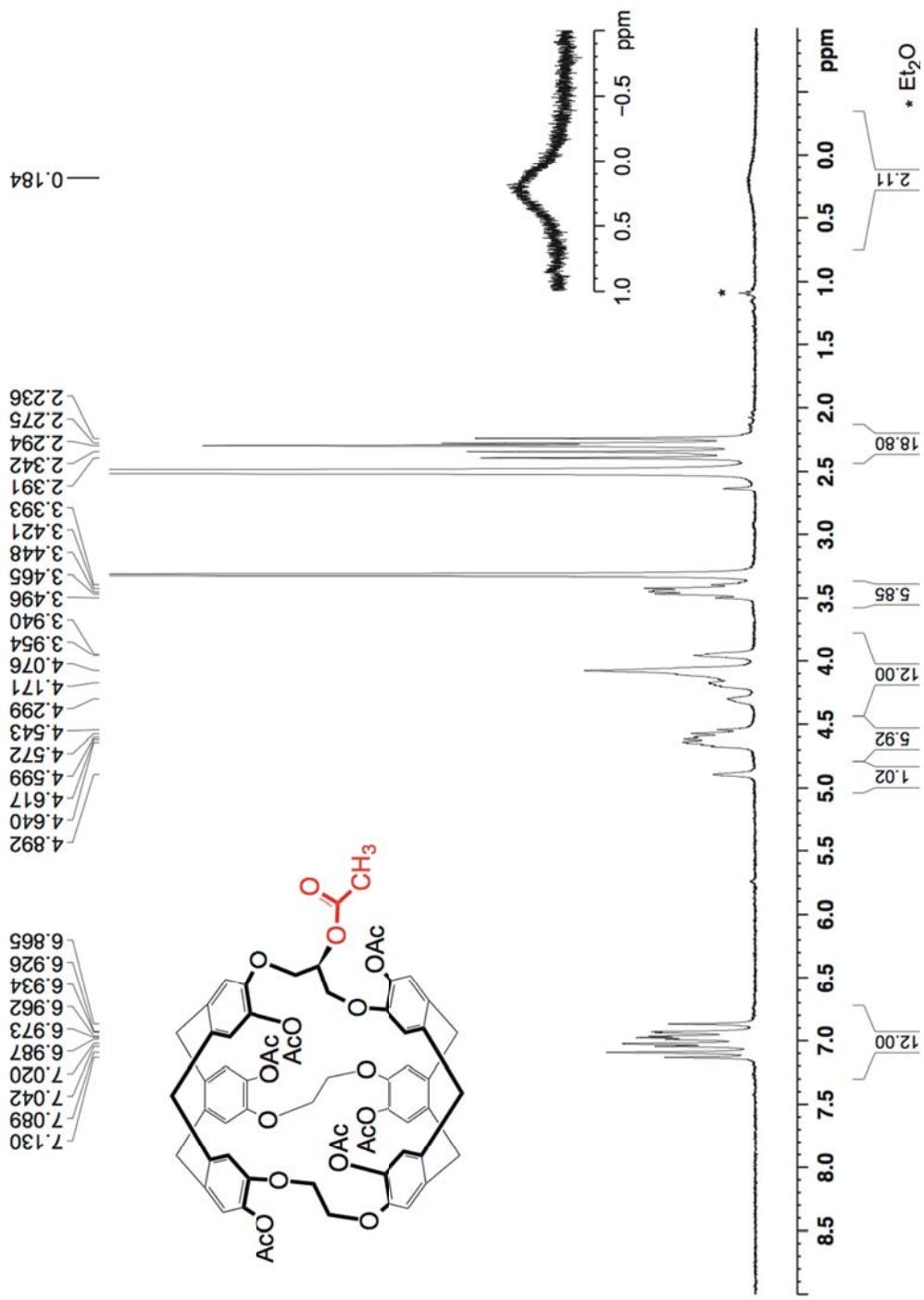


Figure S11: ^1H NMR spectrum (300 MHz) of (rac)-**1** recorded in $\text{DMSO}-d_6$ at 25 °C.

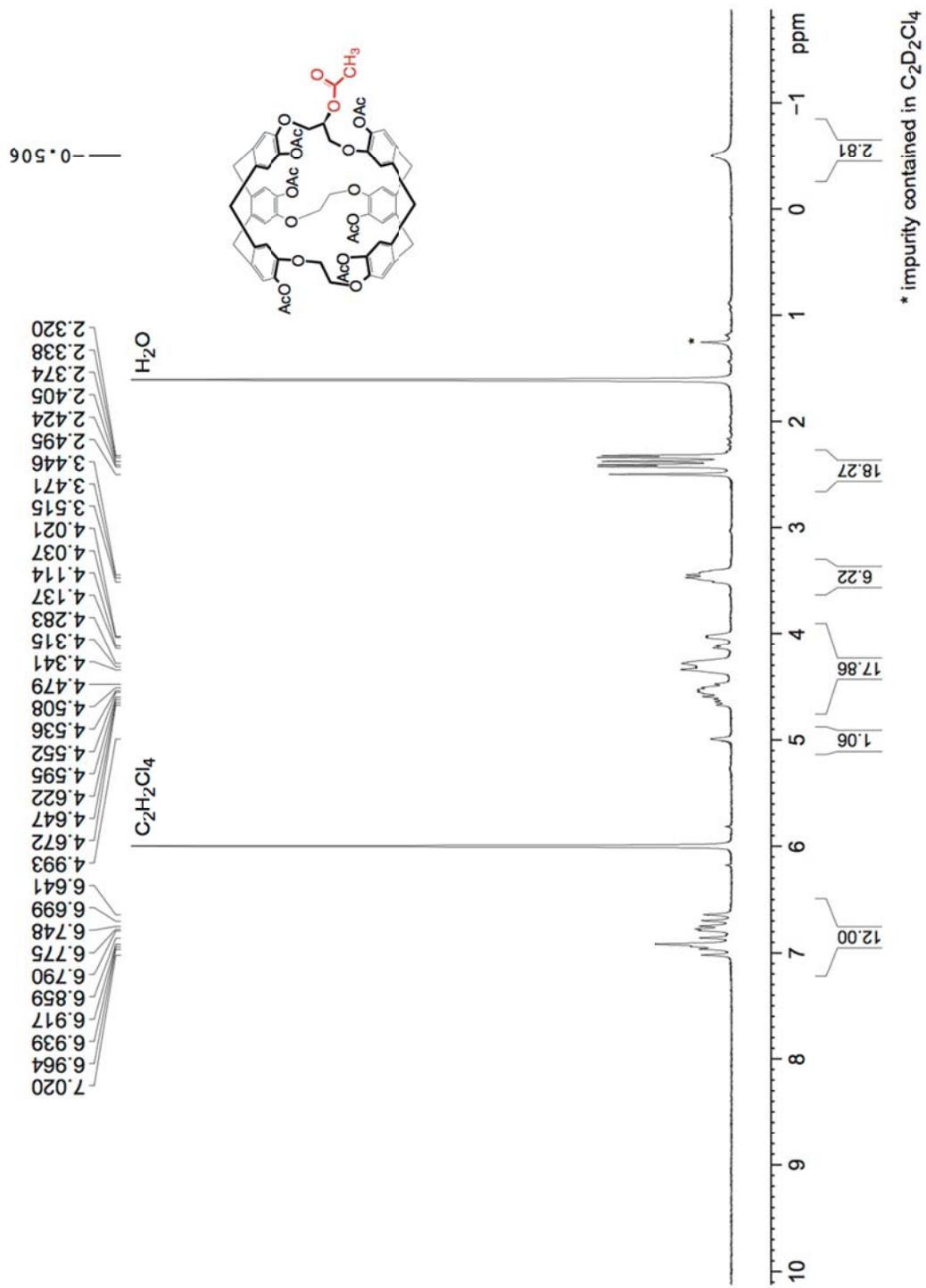


Figure S12: ^1H NMR spectrum (300 MHz) of (rac)-**1** recorded in 1,1,2,2-tetrachloroethane- d_2 at 25 °C.

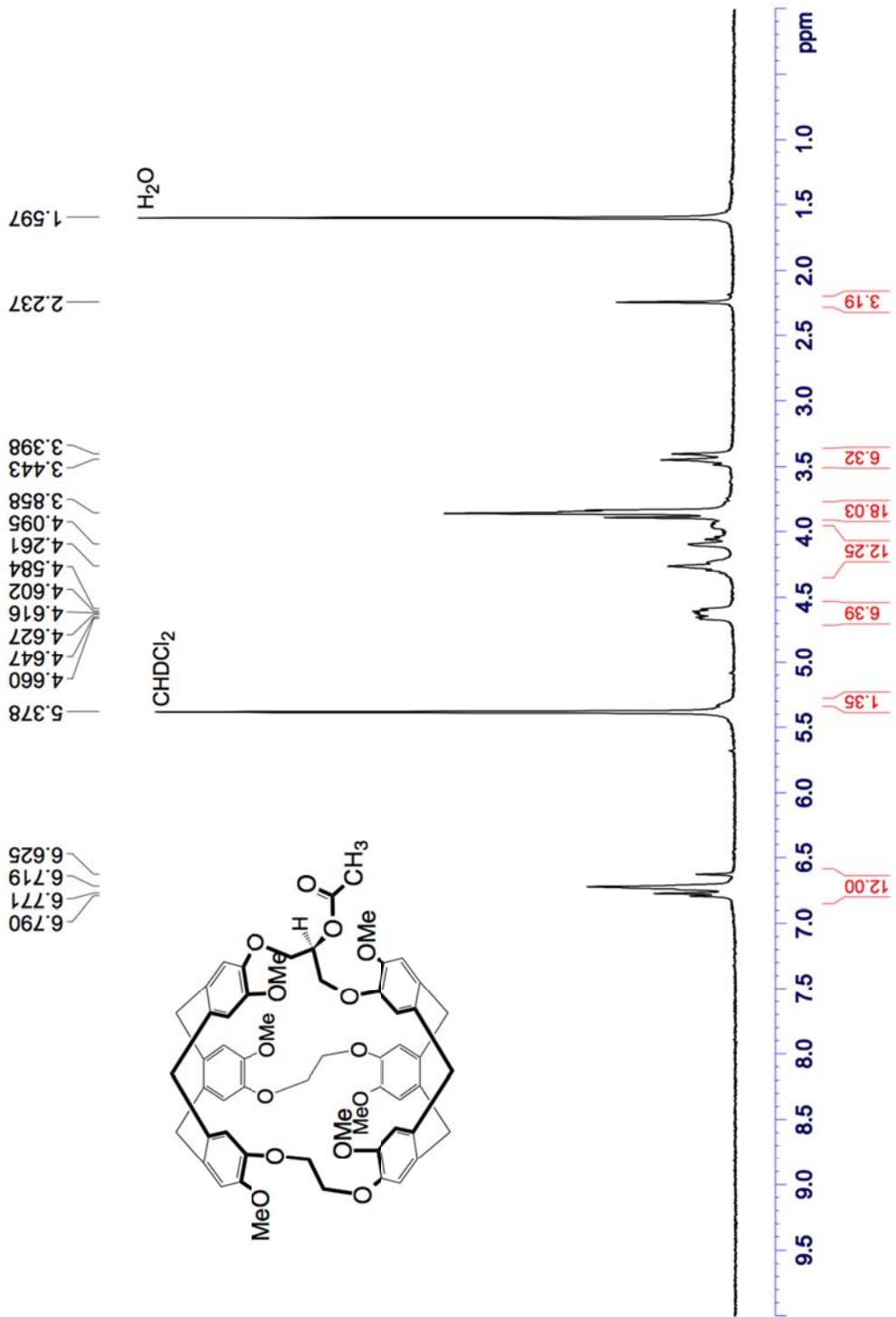


Figure S13: ¹H NMR spectrum (300 MHz) of (rac)-2 recorded in CD_2Cl_2 at 25°C .

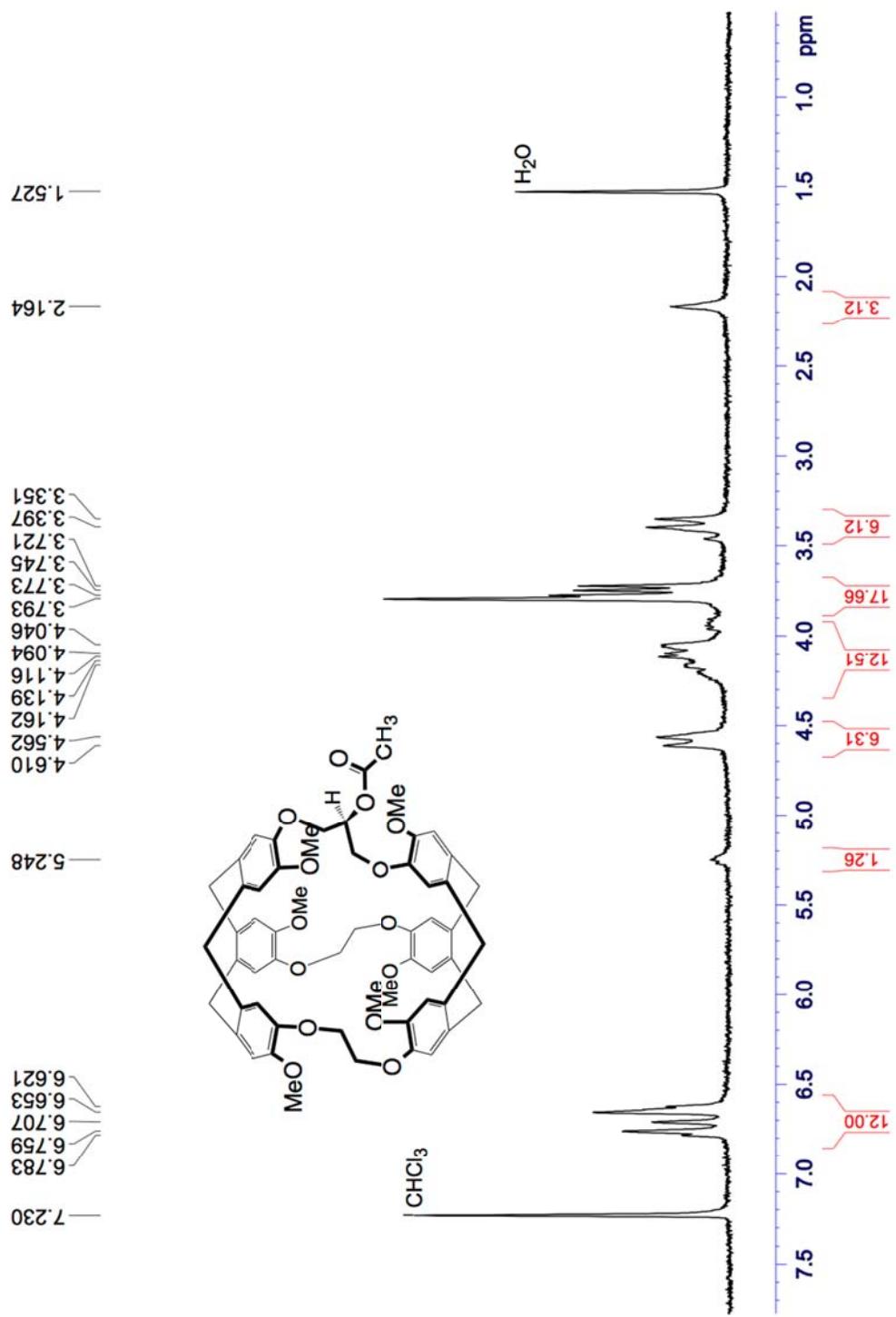


Figure S14: ^1H NMR spectrum (300 MHz) of (rac)-2 recorded in CDCl_3 at 25 °C.

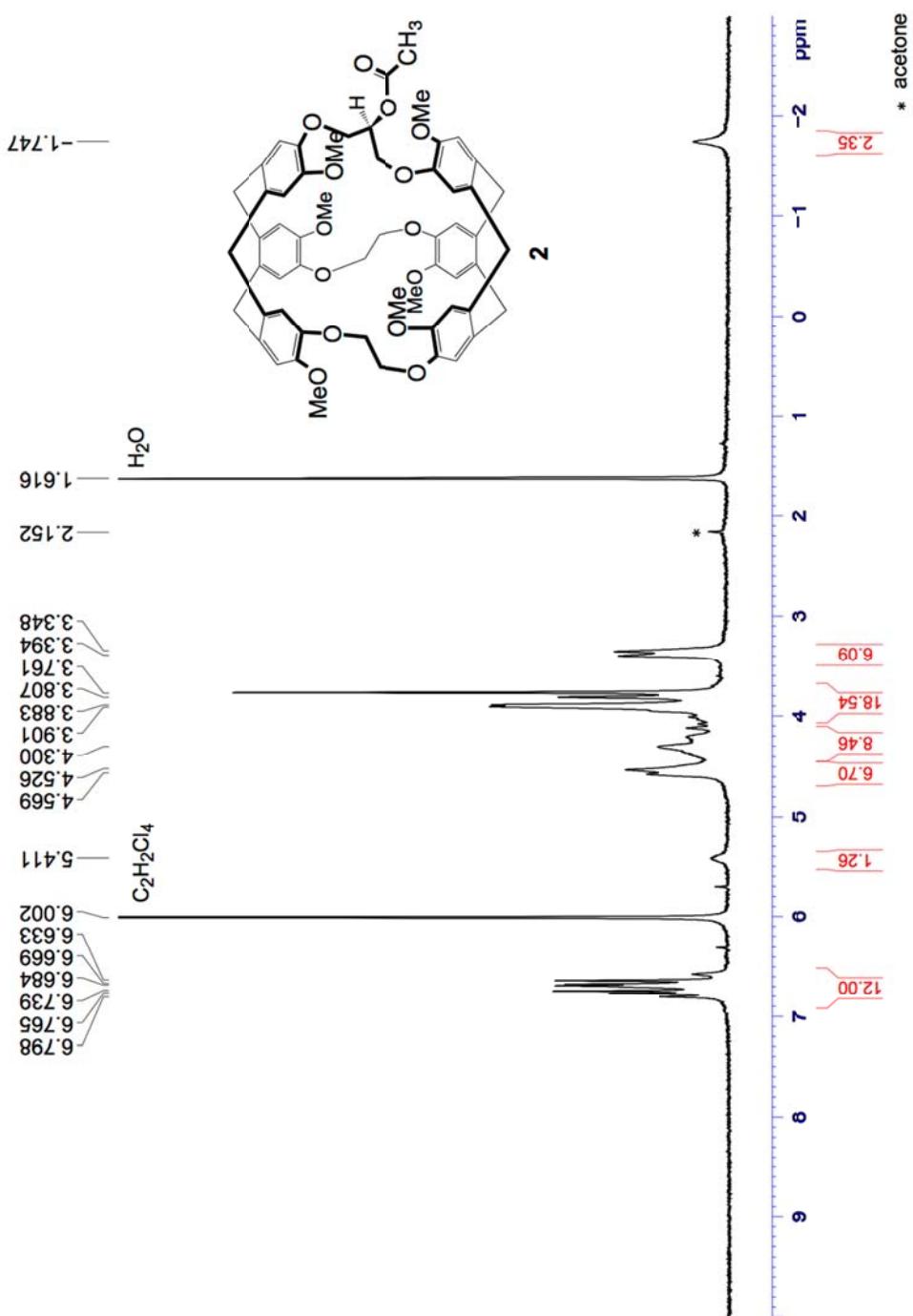


Figure S15: ^1H NMR spectrum (300 MHz) of (rac)-**2** recorded in 1,1,2,2-tetrachloroethane- d_2 at 25 °C.

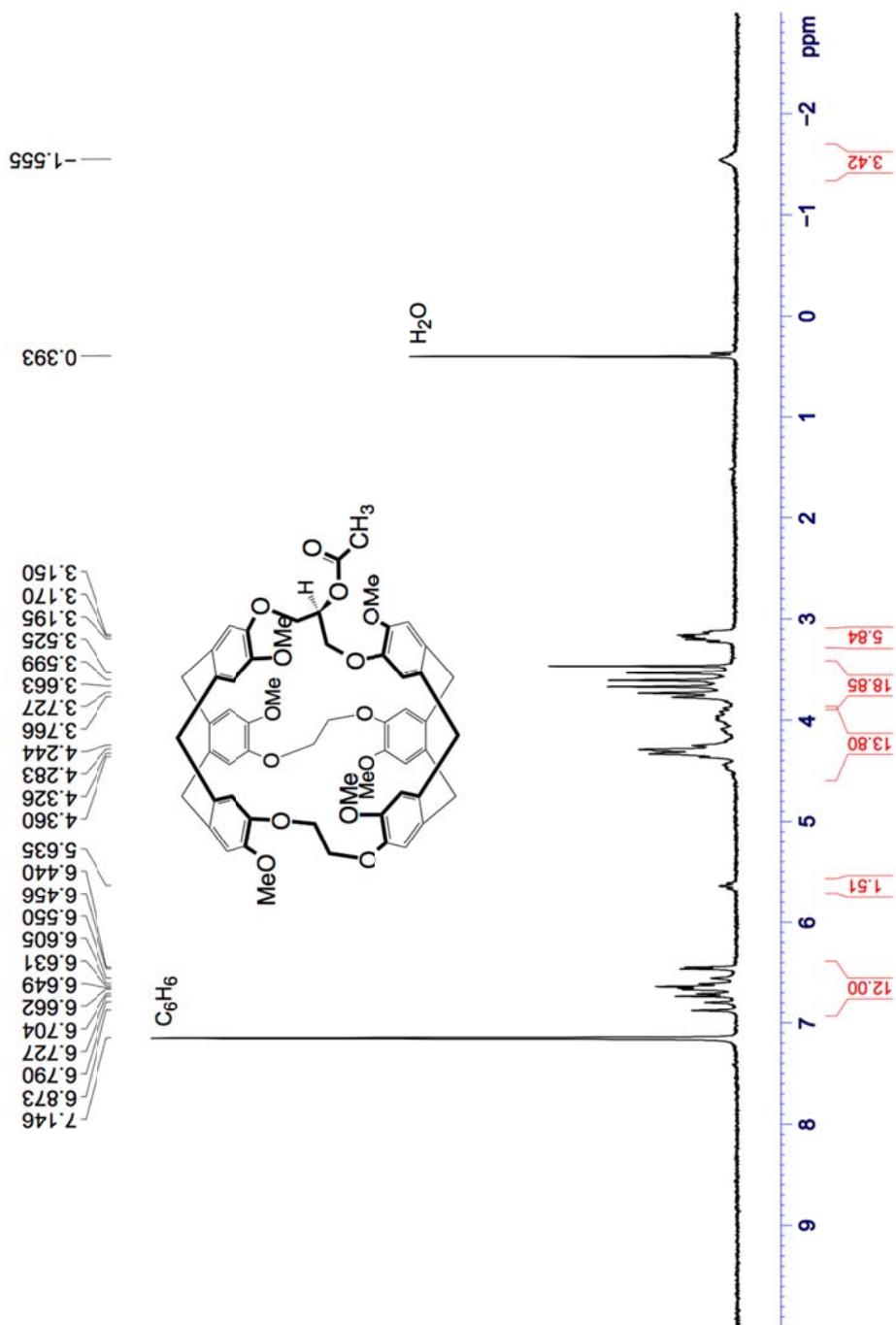


Figure S16: ^1H NMR spectrum (300 MHz) of (rac)-2 recorded in benzene- d_6 at 25 °C.

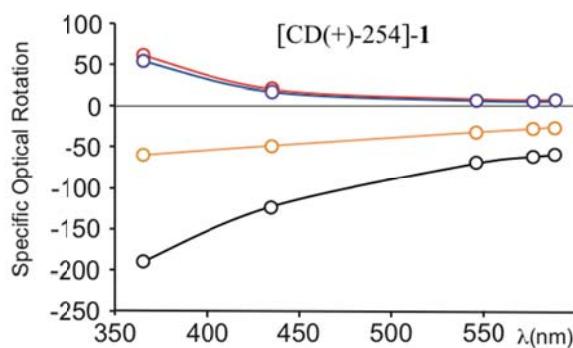


Figure S17: Specific Optical Rotation (SOR) values measured for $[CD(+)-254]\text{-1}$ and $[CD(-)-254]\text{-1}$ in CH_2Cl_2 (black), CHCl_3 (orange), DMSO (blue) and $\text{C}_2\text{H}_2\text{Cl}_4$ (red) at 25 °C. Plot of the SOR ($10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$) values versus λ (nm) for the $[CD(+)-254]\text{-1}$ enantiomer.

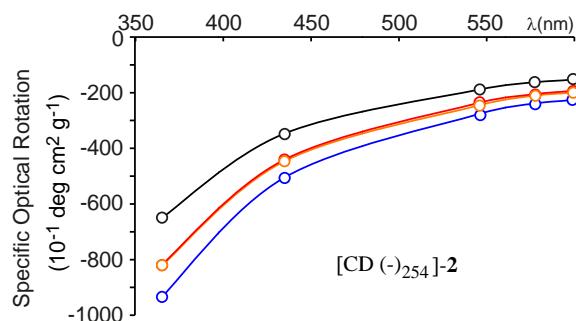


Figure S18: Specific Optical Rotation (SOR) values measured for $[CD(+)-254]\text{-2}$ and $[CD(-)-254]\text{-2}$ in CH_2Cl_2 (black), CHCl_3 (orange), DMSO (blue) and $\text{C}_2\text{H}_2\text{Cl}_4$ (red) at 25 °C. Plot of the SOR ($10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$) values versus λ (nm) for the $[CD(+)-254]\text{-2}$ enantiomer.

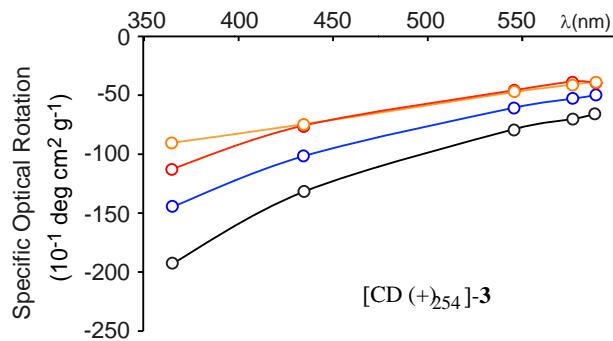


Figure S19: Specific Optical Rotation (SOR) values measured for $[CD(+)-254]\text{-3}$ and $[CD(-)-254]\text{-3}$ in CH_2Cl_2 (black), CHCl_3 (orange), DMSO (blue) and $\text{C}_2\text{H}_2\text{Cl}_4$ (red) at 25 °C. Plot of the SOR ($10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$) values versus λ (nm) for the $[CD(+)-254]\text{-3}$ enantiomer.

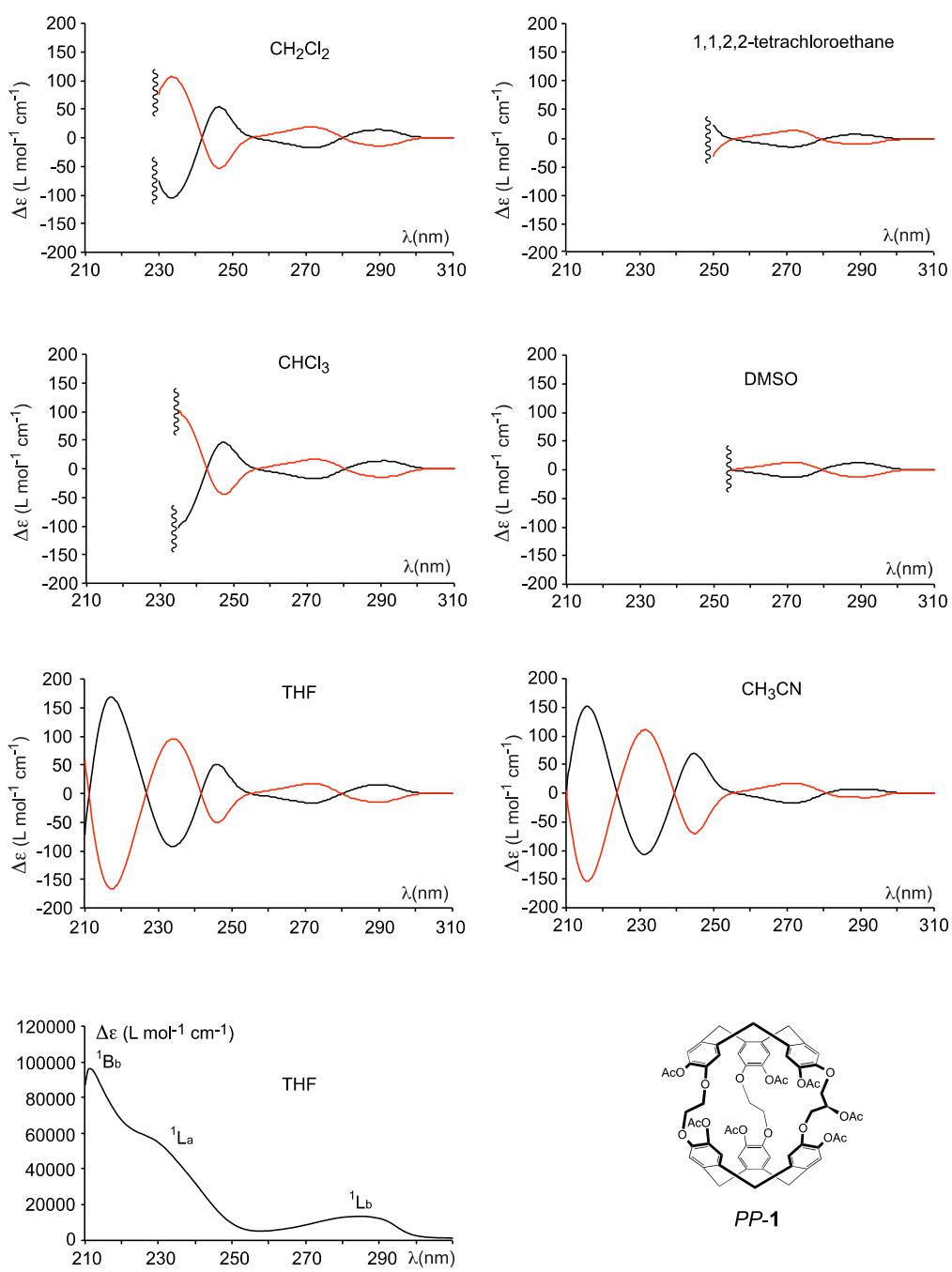


Figure S20: ECD spectra of $[\text{CD}(+)]_{254}\text{-1}$ (black spectra) and $[\text{CD}(-)]_{254}\text{-1}$ (red spectra) recorded in CH_2Cl_2 , CHCl_3 , THF, CH_3CN , DMSO and $\text{C}_2\text{H}_2\text{Cl}_4$ at 20°C . ($c = 10^{-4} - 10^{-5} \text{ M}$). UV-visible spectrum of **1** recorded in THF at 25°C ($c = 1.12 \cdot 10^{-5} \text{ M}$).

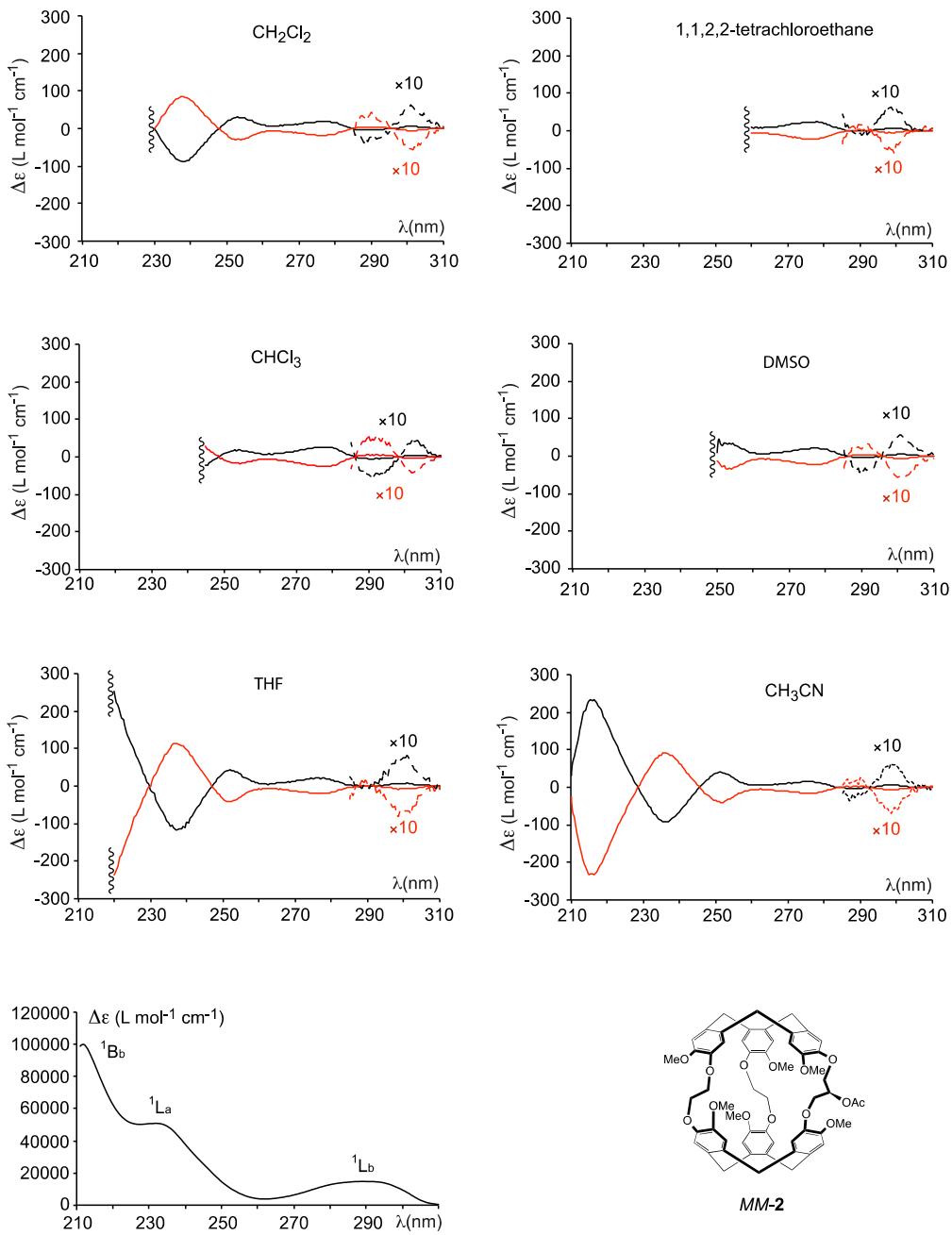


Figure S21: ECD spectra of $[\text{CD}(+)]_{254}\text{-2}$ (black spectra) and $[\text{CD}(-)]_{254}\text{-2}$ (red spectra) recorded in CH_2Cl_2 , CHCl_3 , THF, CH_3CN , DMSO and $\text{C}_2\text{H}_2\text{Cl}_4$ at 20 °C. ($c = 10^{-4} - 10^{-5} \text{ M}$). UV-visible spectrum of **2** recorded in THF at 25 °C ($c = 1.02 \times 10^{-5} \text{ M}$).

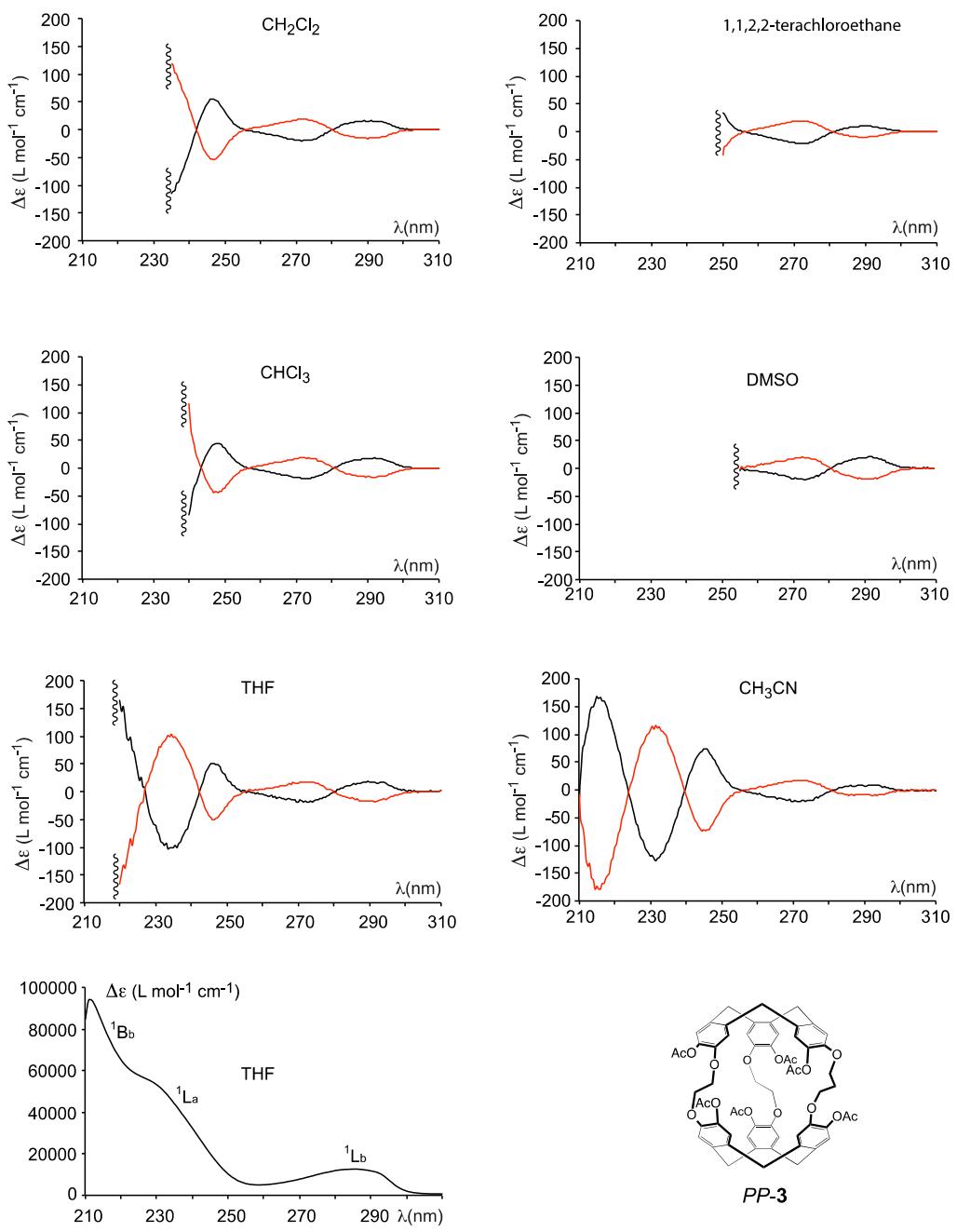


Figure S22: ECD spectra of $[\text{CD}(+)]_{254}\text{-3}$ (black spectra) and $[\text{CD}(-)]_{254}\text{-3}$ (red spectra) recorded in CH_2Cl_2 , CHCl_3 , THF, CH_3CN , DMSO and $\text{C}_2\text{H}_2\text{Cl}_4$ at 20 °C. ($c = 10^{-4} - 10^{-5} \text{ M}$). UV-visible spectrum of **3** recorded in THF at 25 °C ($c = 0.99 \times 10^{-5} \text{ M}$).

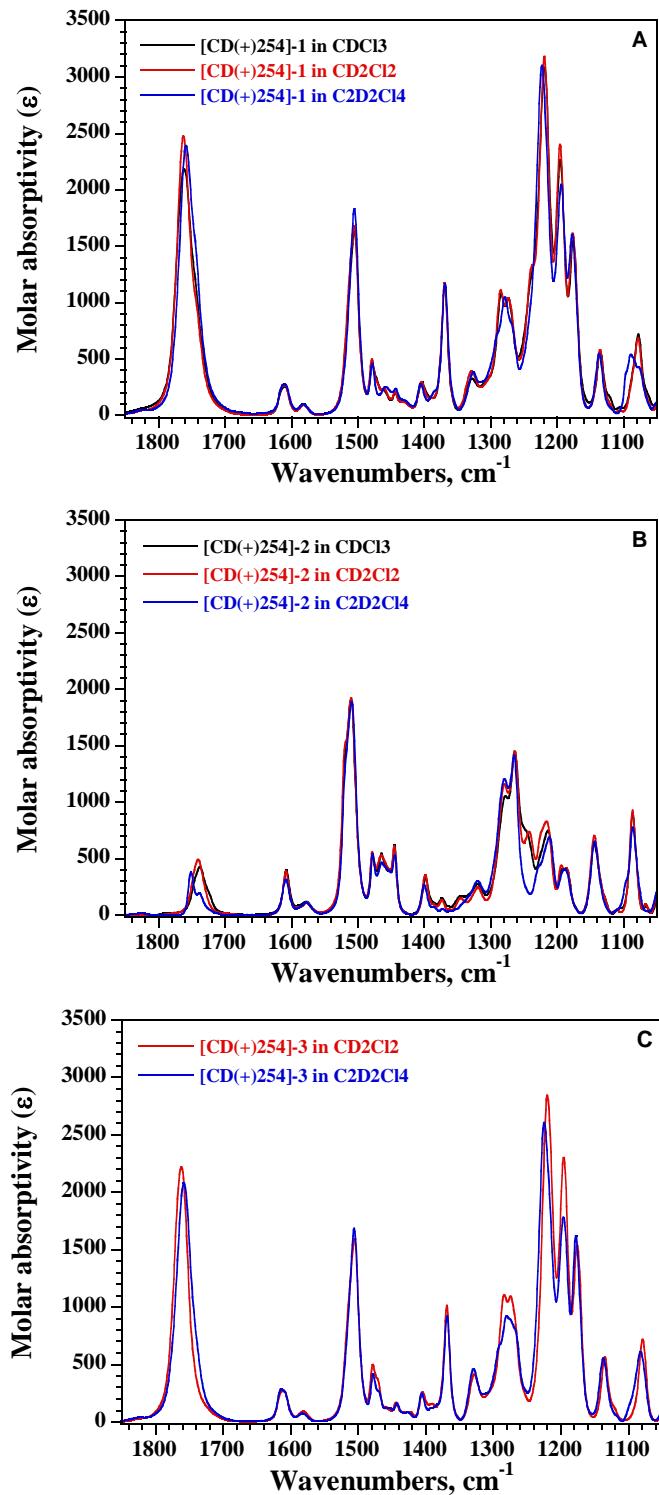


Figure S23: IR spectra of a) $[\text{CD}(+)_\text{254}]\text{-1}$, b) $[\text{CD}(+)_\text{254}]\text{-2}$ and $[\text{CD}(+)_\text{254}]\text{-3}$ c) in CDCl_3 (black spectra), CD_2Cl_2 (red spectra) and $\text{C}_2\text{D}_2\text{Cl}_4$ (blue spectra) solvents (0.015 mM, 250 μm path length).

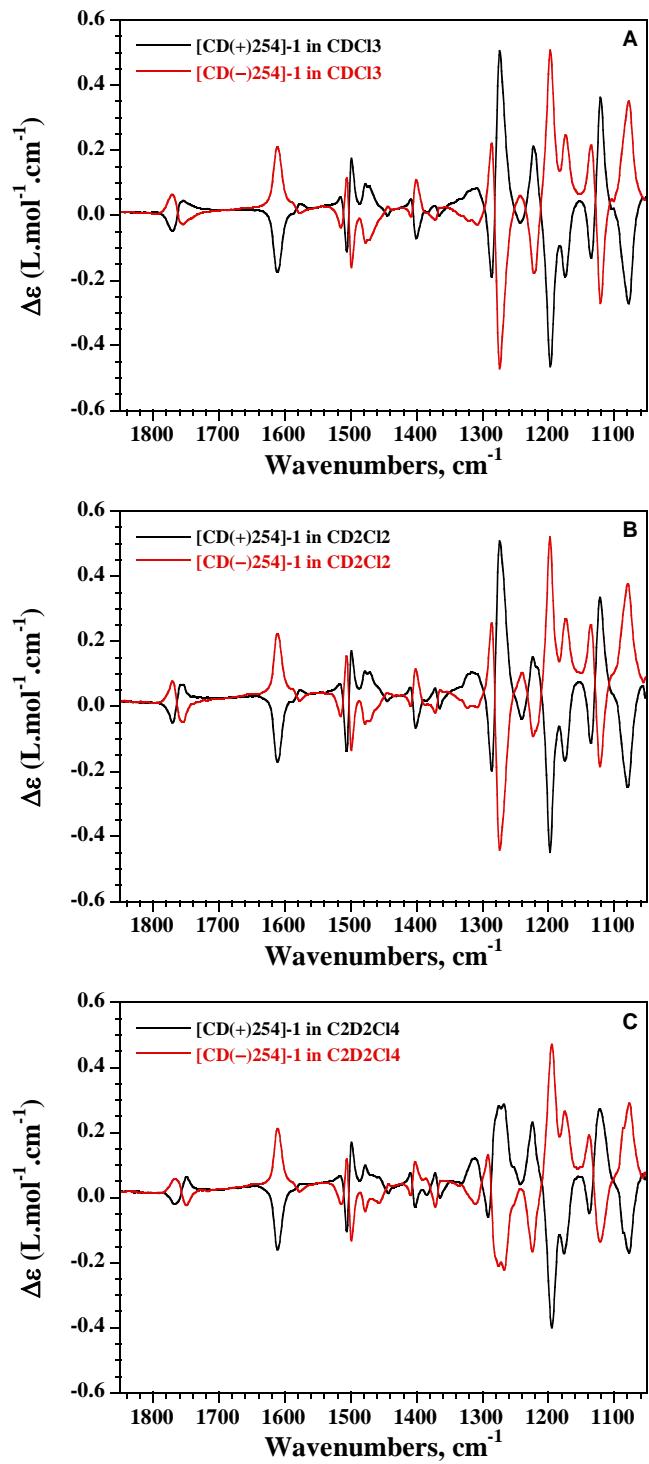


Figure S24: VCD spectra of $[CD(+)_254]\text{-1}$ (black spectra) and $[CD(-)_254]\text{-1}$ (red spectra) in a) CDCl_3 , b) CD_2Cl_2 , and c) $\text{C}_2\text{D}_2\text{Cl}_4$ solvents (0.015 mM, 250 μm path length).

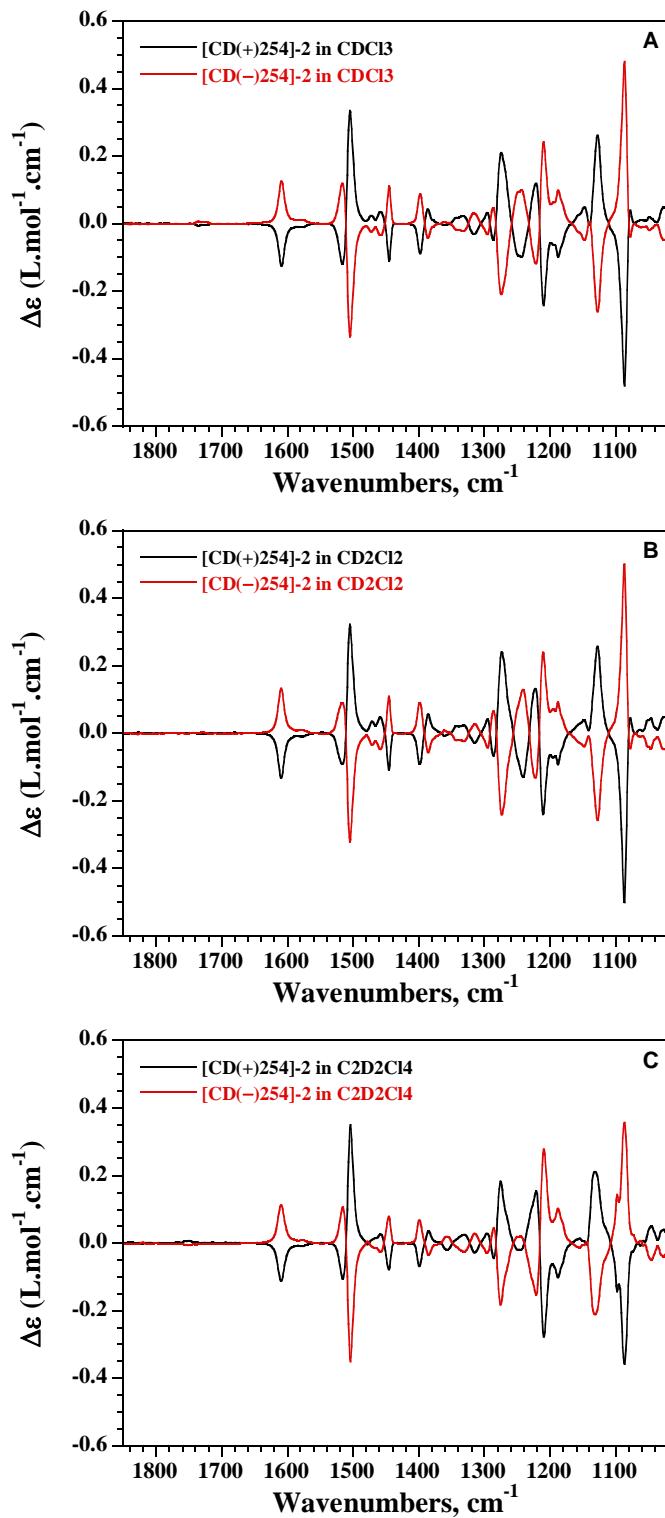


Figure S25: VCD spectra of $[\text{CD}(+)_\text{254}]\text{-2}$ (black spectra) and $[\text{CD}(-)_\text{254}]\text{-2}$ (red spectra) in a) CDCl_3 , b) CD_2Cl_2 , and c) $\text{C}_2\text{D}_2\text{Cl}_4$ solvents (0.015 mM, 250 μm path length).

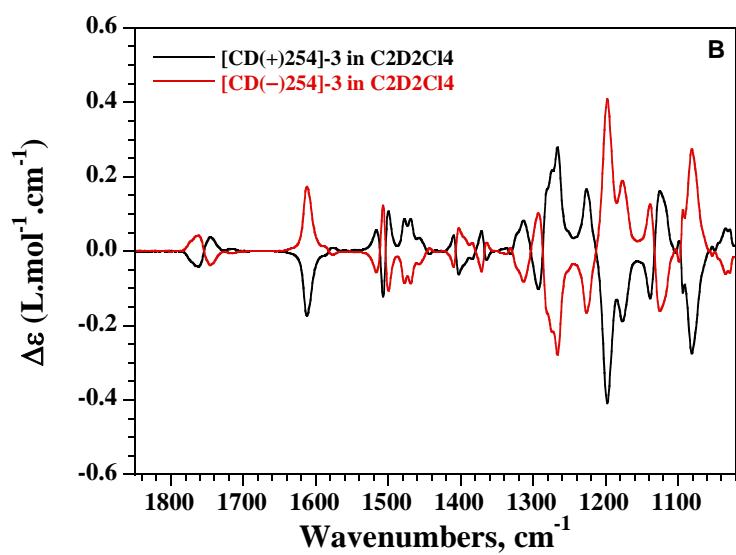
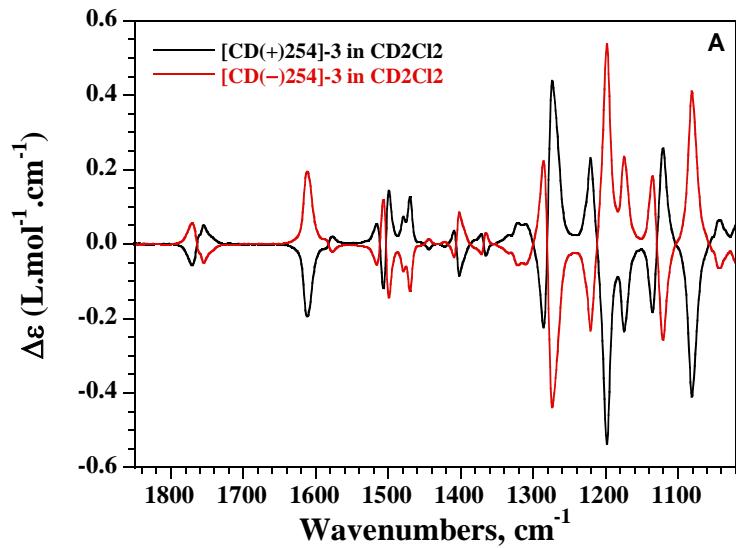
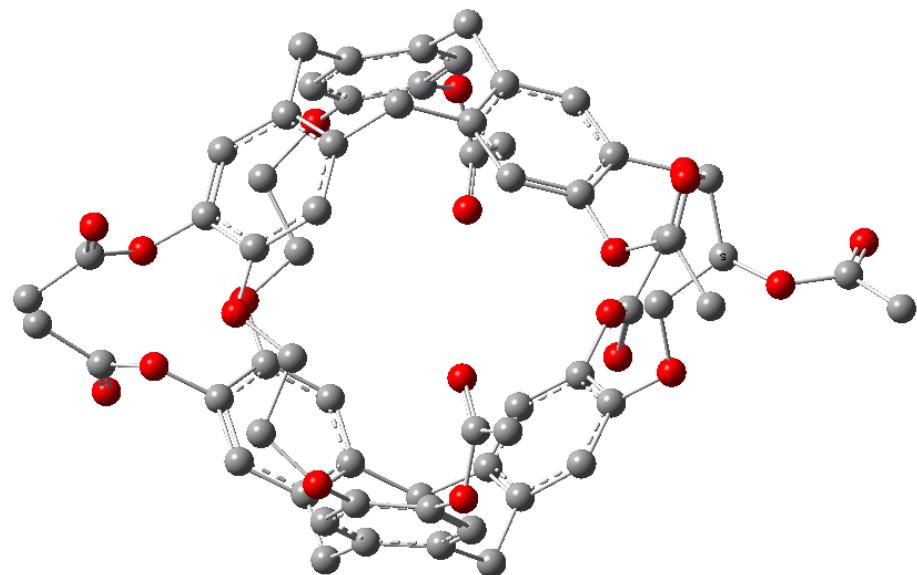


Figure S26: VCD spectra of $[\text{CD}(+)]_3$ (black spectra) and $[\text{CD}(-)]_3$ (red spectra) in a) CD_2Cl_2 and b) $\text{C}_2\text{D}_2\text{Cl}_4$ solvents (0.015 mM, 250 μm path length).

a) Optimized structure of *PP-1*: (IEFPCM = CH₂Cl₂)



b) Optimized structure of *PP-1*: (IEFPCM = C₂H₂Cl₄)

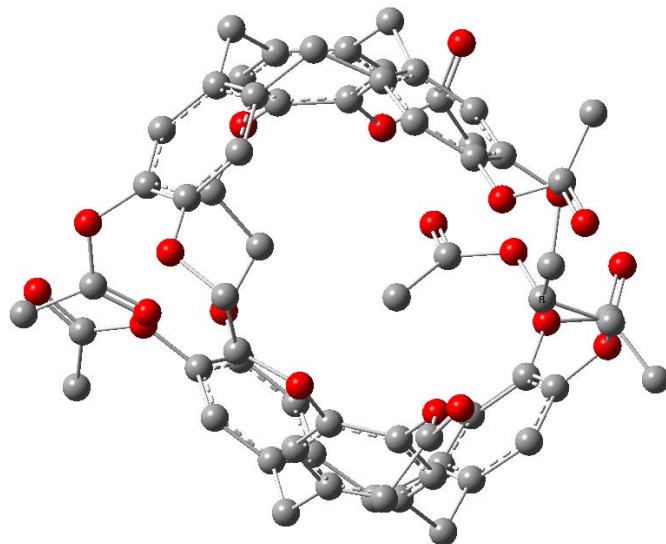
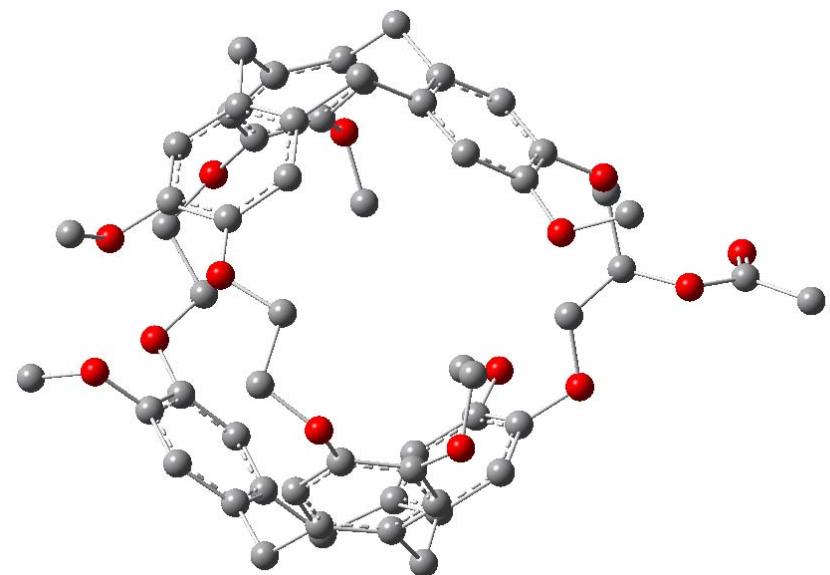


Figure S27: Optimized geometry of *PP-1* enantiomer calculated at the density functional theory (DFT) level using B3LYP functional and 6-31G** basis set with the use of IEFPCM model of solvent (IEFPCM = CH₂Cl₂ and C₂H₂Cl₄).

a) Optimized structure of *MM-2*: (IEFPCM = CH₂Cl₂)



b) Optimized structure of *MM-2*: (IEFPCM = C₂H₂Cl₄)

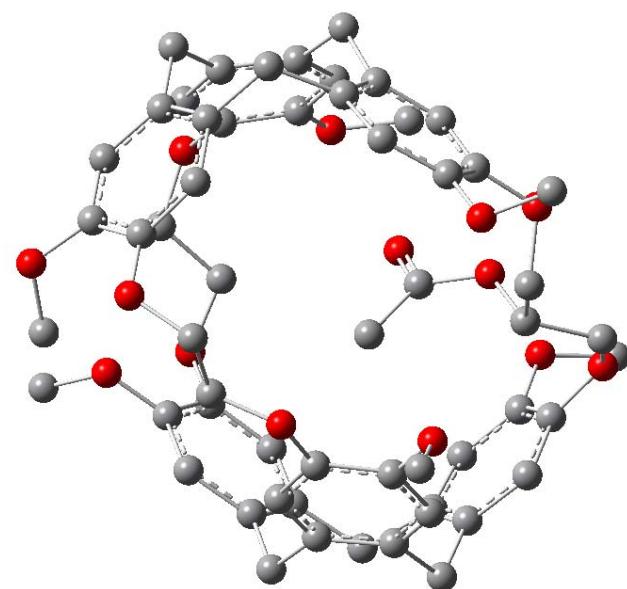


Figure S28: Optimized geometry of *MM-2* enantiomer calculated at the density functional theory (DFT) level using B3LYP functional and 6-31G** basis set with the use of IEFPCM model of solvent (IEFPCM = CH₂Cl₂ and C₂H₂Cl₄).

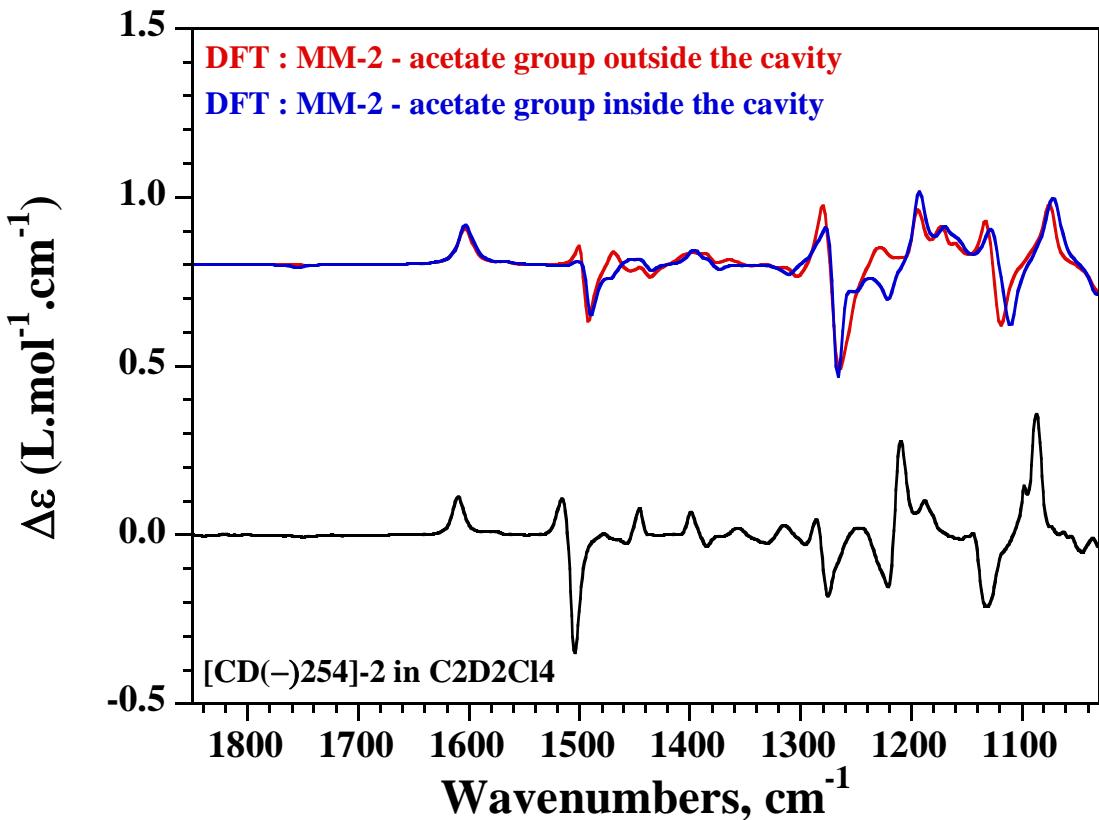


Figure S29: Comparison of experimental VCD spectrum of [CD(-)₂₅₄]-2 in C₂D₂Cl₄ solution (15 mM, 250 μ m path length) and VCD spectra of *MM-2* calculated at the B3LYP/6-31G** level (IEFPCM = C₂H₂Cl₄) for the *trans* and *gauche-gauche* conformations of the ethylenedioxy and propylenedioxy linkers, respectively, and for the acetate group grafted on the propylenedioxy linker pointing inside (blue spectrum) or outside (red spectrum) the cavity.

Table S1: Specific optical rotation values measured for $[CD(+)]_{254}$ -**1** in different solvents at 25 °C.

Solvent	Conc.	$[\alpha]_{589}$	$[\alpha]_{577}$	$[\alpha]_{546}$	$[\alpha]_{435}$	$[\alpha]_{365}$
CH ₂ Cl ₂	0.21	-60.1	-62.3	-70.3	-123.4	-190.9
CHCl ₃	0.23	-25.4	-28.3	-32.1	-48.5	-59.8
DMSO	0.26	+7.2	+7.0	+8.0	+19.9	+61.4
C ₂ H ₂ Cl ₄	0.26	+8.1	+9.1	+12.0	+23.4	+66.3

Table S2: Specific optical rotation values measured for $[CD(-)]_{254}$ -**1** in different solvents at 25 °C.

Solvent	Conc.	$[\alpha]_{589}$	$[\alpha]_{577}$	$[\alpha]_{546}$	$[\alpha]_{435}$	$[\alpha]_{365}$
CH ₂ Cl ₂	0.21	+58.4	+62.0	+70.3	+121.2	+188.2
CHCl ₃	0.25	+23.9	+24.9	+28.4	+46.9	+57.3
DMSO	0.26	-7.6	-8.9	-9.7	-23.4	-66.1
C ₂ H ₂ Cl ₄	0.29	-10.4	-9.8	-13.6	-26.2	-64.4

Table S3: Specific optical rotation values measured for $[CD(+)]_{254}$ -**2** in different solvents at 25 °C.

Solvent	Conc.	$[\alpha]_{589}$	$[\alpha]_{577}$	$[\alpha]_{546}$	$[\alpha]_{435}$	$[\alpha]_{365}$
CH ₂ Cl ₂	0.19	+159.0	+168.0	+194.5	+359.0	+664.5
CHCl ₃	0.26	+201.0	+214.1	+246.5	+453.5	+845.1
DMSO	0.31	+228.3	+241.1	+278.8	+510.4	+943.5
C ₂ H ₂ Cl ₄	0.21	+199.0	+213.0	+244.5	+448.0	+835.5

Table S4: Specific optical rotation values measured for $[CD(-)]_{254}$ -**2** in different solvents at 25 °C.

Solvent	Conc.	$[\alpha]_{589}$	$[\alpha]_{577}$	$[\alpha]_{546}$	$[\alpha]_{435}$	$[\alpha]_{365}$
CH ₂ Cl ₂	0.24	-155.0	-163.0	-189.0	-347.0	-652.0
CHCl ₃	0.27	-200.2	-211.0	-245.0	-446.4	-823.4
DMSO	0.30	-227.8	-239.0	-276.4	-505.0	-936.0
C ₂ H ₂ Cl ₄	0.20	-192.5	-206.0	-236.5	-440.5	-820.0

Table S5: Specific optical rotation values measured for $[CD(+)]_{254}$ -**3** in different solvents at 25 °C.

Solvent	Conc.	$[\alpha]_{589}$	$[\alpha]_{577}$	$[\alpha]_{546}$	$[\alpha]_{435}$	$[\alpha]_{365}$
CH ₂ Cl ₂	0.26	-66.0	-70.1	-78.7	-131.6	-191.3
CHCl ₃	0.24	-38.6	-40.9	-47.3	-74.5	-90.4
DMSO	0.25	-50.0	-52.9	-60.5	-101.5	-145.0
DMF	0.27	-53.9	-54.8	-61.8	-102.6	-142.3
C ₂ H ₂ Cl ₄	0.30	-38.9	-38.3	-45.7	-75.6	-112.7

Table S6: Specific optical rotation values measured for $[CD(-)]_{254}$ -**3** in different solvents at 25 °C.

Solvent	Conc.	$[\alpha]_{589}$	$[\alpha]_{577}$	$[\alpha]_{546}$	$[\alpha]_{435}$	$[\alpha]_{365}$
CH ₂ Cl ₂	0.25	+62.8	+64.5	+72.9	+122.0	+176.8
CHCl ₃	0.29	+35.2	+38.0	+42.3	+68.0	+82.5
DMSO	0.26	+47.0	+49.0	+54.8	+92.2	+127.5
DMF	0.26	+45.3	+49.4	+55.0	+88.1	+118.5
C ₂ H ₂ Cl ₄	0.31	+34.0	+35.1	+43.9	+68.2	+102.0

Table S7: B3LYP/6-31G** frequencies (scaled by 0.968) of the ester $\nu C=O$ stretching vibration of **MM-2** (IEFPCM = CH₂Cl₂ and C₂D₂Cl₄) for the acetate group pointing inward or outward the cavity.

	IEFPCM = CH ₂ Cl ₂	IEFPCM = C ₂ D ₂ Cl ₄
Acetate pointing inward the cavity	1753.58	1755.17
Acetate pointing outward the cavity	1741.42	1742.52

Full list of authors of references 25

25 Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision A.1, Gaussian Inc., Wallingford CT, **2009**.