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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

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Chiroptical Study of Cryptophanes Subjected to Self-Encapsulation

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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.

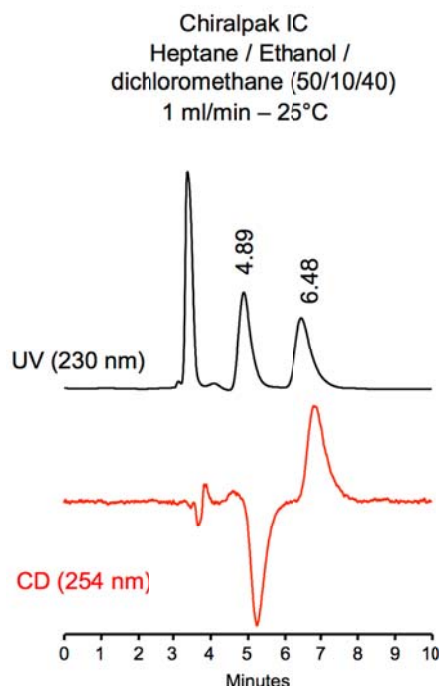
Table S4: Specific optical rotation values measured for [CD(-)₂₅₄]-**2** in different solvents at 25 °C.

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Analytical separation for compound **1**



Column	Mobile Phase	t_1	k_1	t_2	k_2	α	R_s
Chiralpak 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 (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).

Semi-preparative separation for compound **1**

Sample preparation: About 460 mg of compound (rac)-**1** are dissolved in 18 mL of dichloromethane. Chromatographic conditions: Chiralpak 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 μ L, 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

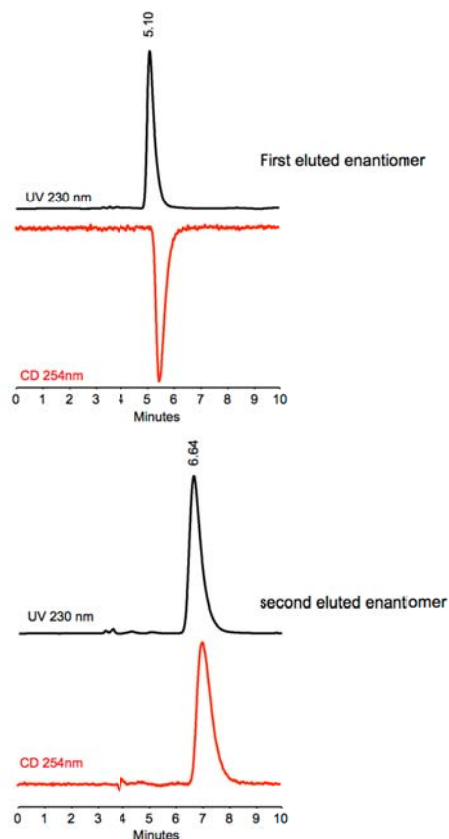
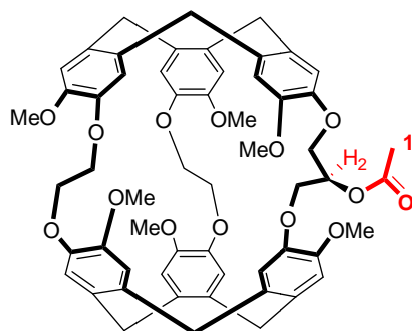
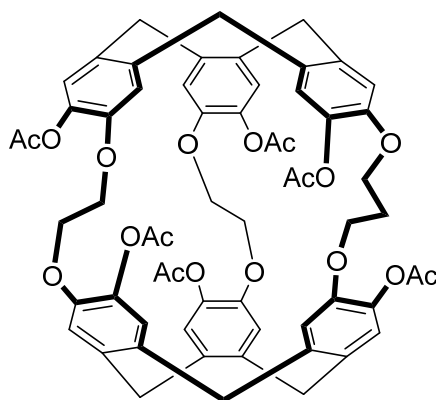


Figure S2: Chromatograms (Chiralpak IC, 250 x 4.6 mm, heptane/ethanol/CH₂Cl₂: 50/10/40, 1 mL/min at 25 °C) of the collected [CD(-)₂₅₄]-**1** and [CD(+)₂₅₄]-**1** after preparative separation on Chiralpak IC (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 50/10/40, 5 mL/min). Detection performed by UV-Vis spectroscopy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

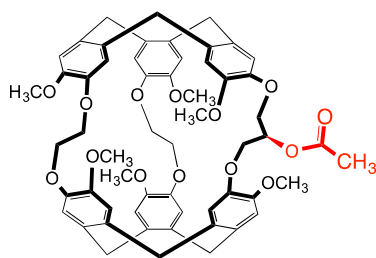
Figure S3: Experimental procedure for the synthesis of cryptophane **2**.



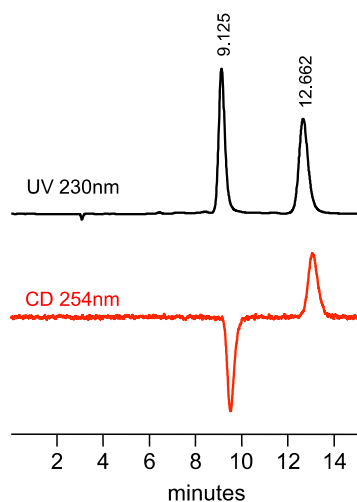
Synthesis of cryptophane 3: Acetic anhydride (2.2 mL, 41 mmol) was added dropwise at 0 °C to a solution of cryptophane223(OH)₆ (0.35g, 0.42 mmol) in Pyridine (5 mL). The reaction was stirred at room temperature for 16 hours under an argon atmosphere. Then, the reaction was quenched with a solution of 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	t ₁	k ₁	t ₂	k ₂	α	Rs
(<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.

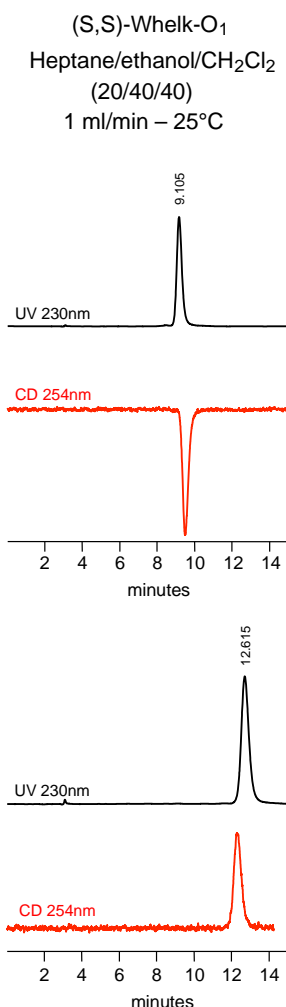
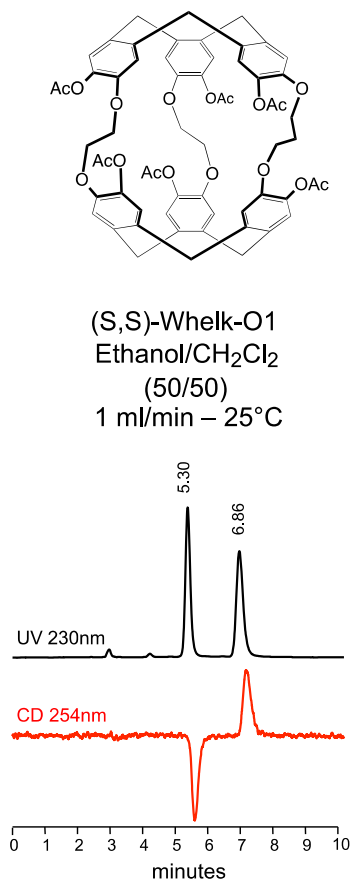


Figure S6: Chromatograms ((*S,S*)-Whelk-O₁, 250 x 4.6 mm, heptane/ethanol/CH₂Cl₂: 20/40/40, 1 mL/min at 25 °C) of the collected [CD(-)₂₅₄]-**2** and [CD(+)₂₅₄]-**2** after preparative separation on (*S,S*)-Whelk-O₁ (250 x 10 mm, heptane/ethanol/CH₂Cl₂: 20/40/40, 5 mL/min). Detection performed by UV-Vis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

Analytical separation for compound **3**



Column	Mobile Phase	t ₁	k ₁	t ₂	k ₂	α	Rs
(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 μ L, 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.

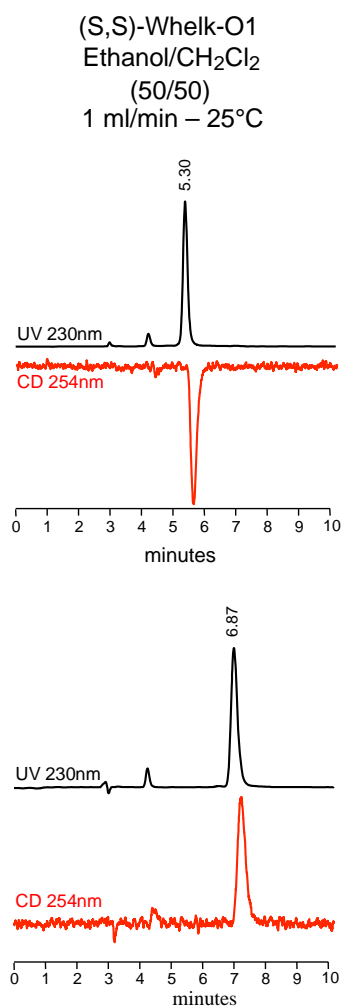


Figure S8: Chromatograms ((*S,S*)-Whelk-O₁, 250 x 4.6 mm, ethanol/CH₂Cl₂: 50/50, 1 mL/min at 25 °C) of the collected [CD(-)₂₅₄]-**3** and [CD(+)₂₅₄]-**3** after preparative separation on (*S,S*)-Whelk-O₁ (250 x 10 mm, ethanol/CH₂Cl₂: 50/50, 5 mL/min). Detection performed by UV-Vis spectroscopy at 230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

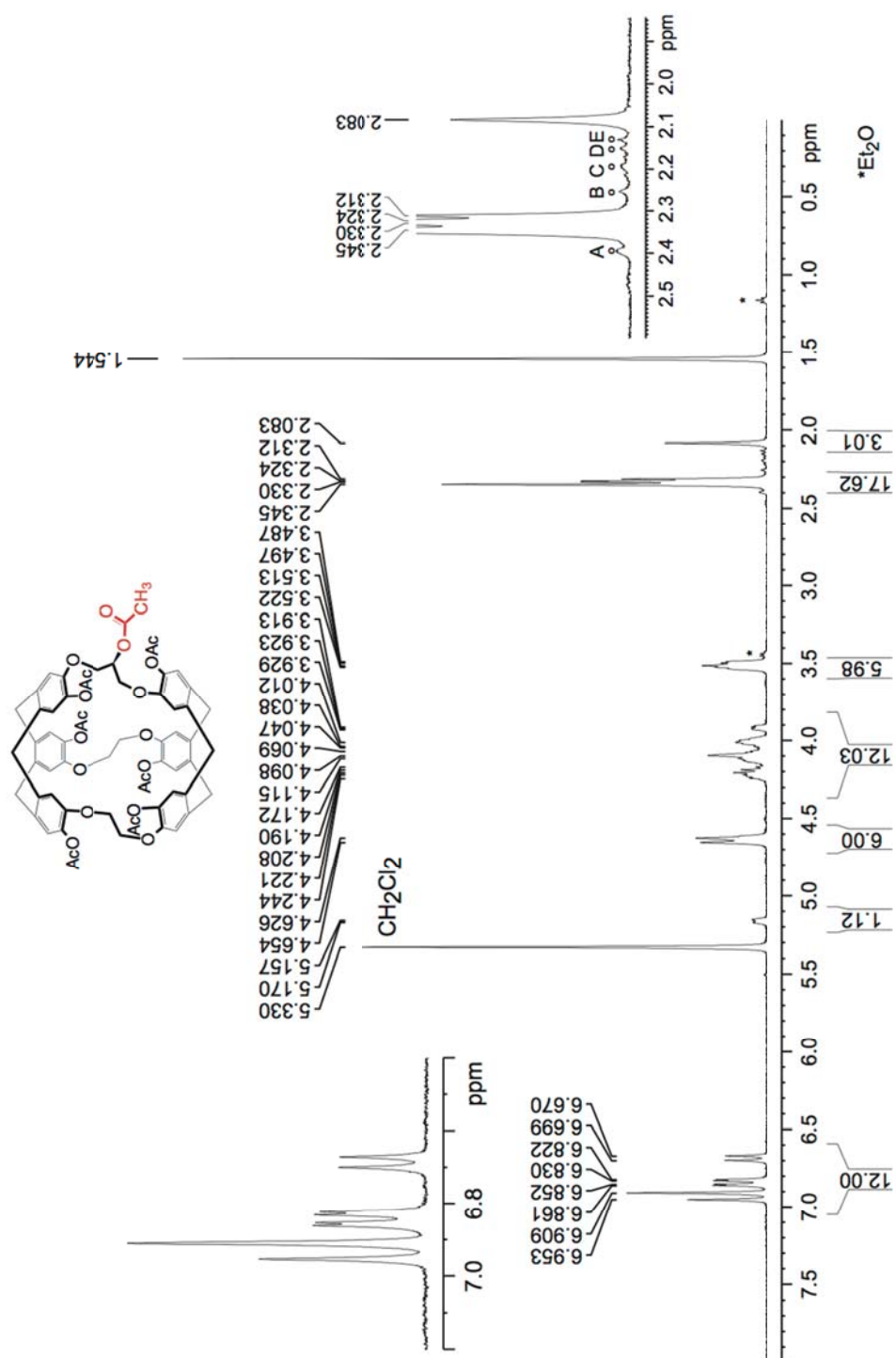


Figure S9: ^1H NMR spectrum (300 MHz) of (rac)-1 recorded in CD_2Cl_2 at 25°C . The letters A,B,C,D,E show protons signals related to the imploded form.

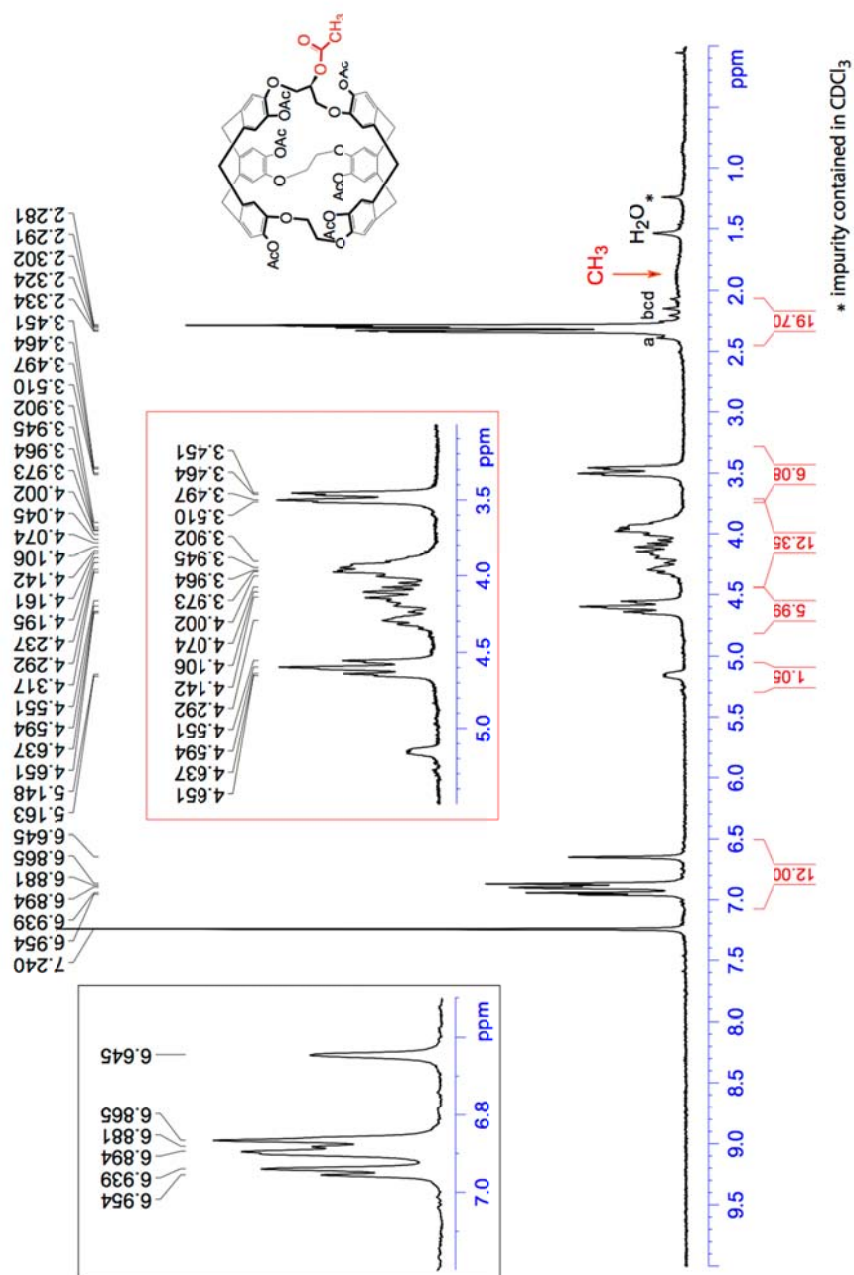


Figure S10: ¹H NMR spectrum (300 MHz) of (rac)-1 recorded in CDCl₃ at 25 °C. The letters A,B,C,D show protons signals related to the imploded form.

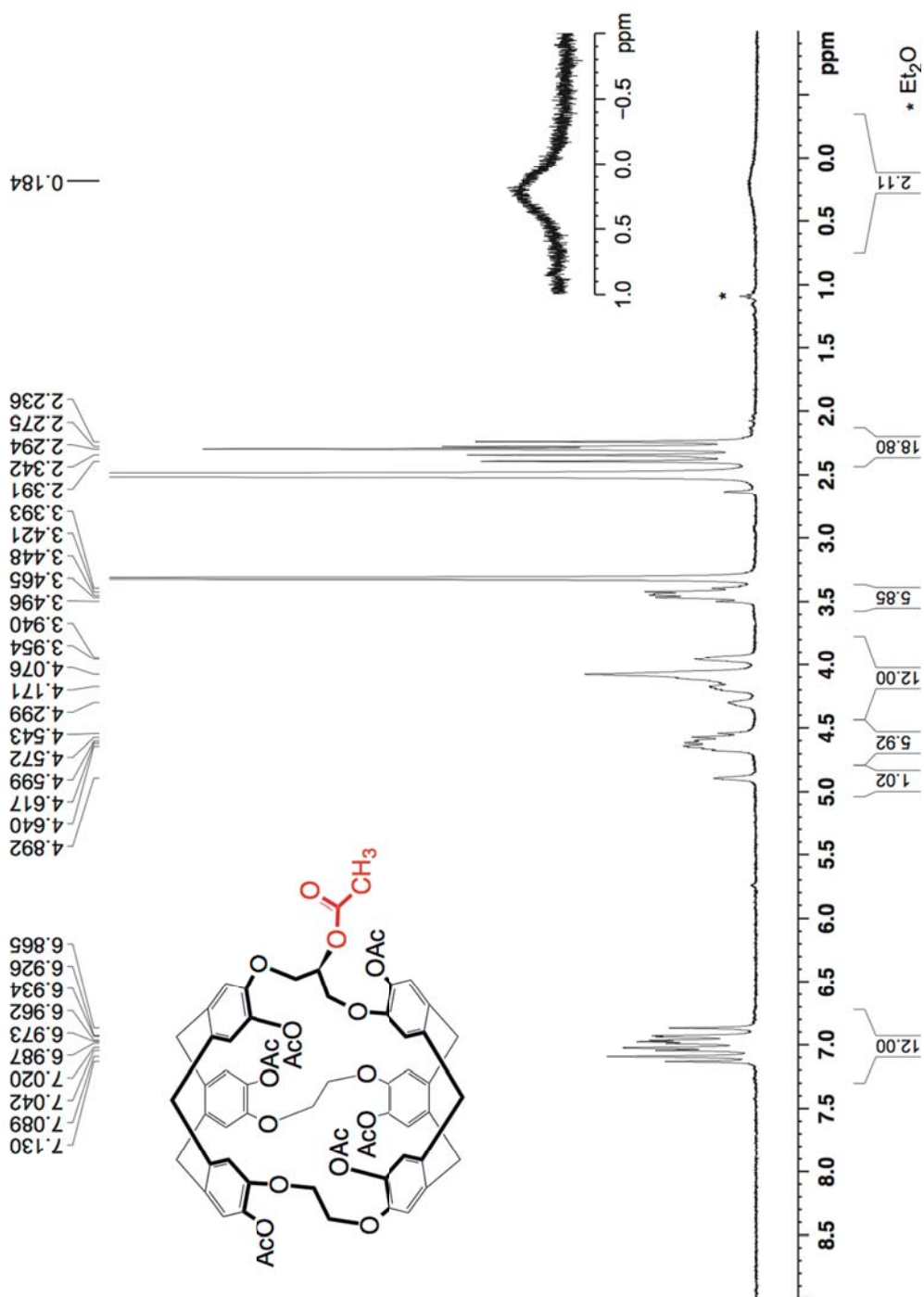


Figure S11: ^1H NMR spectrum (300 MHz) of (rac)-1 recorded in $\text{DMSO-}d_6$ at $25\text{ }^\circ\text{C}$.

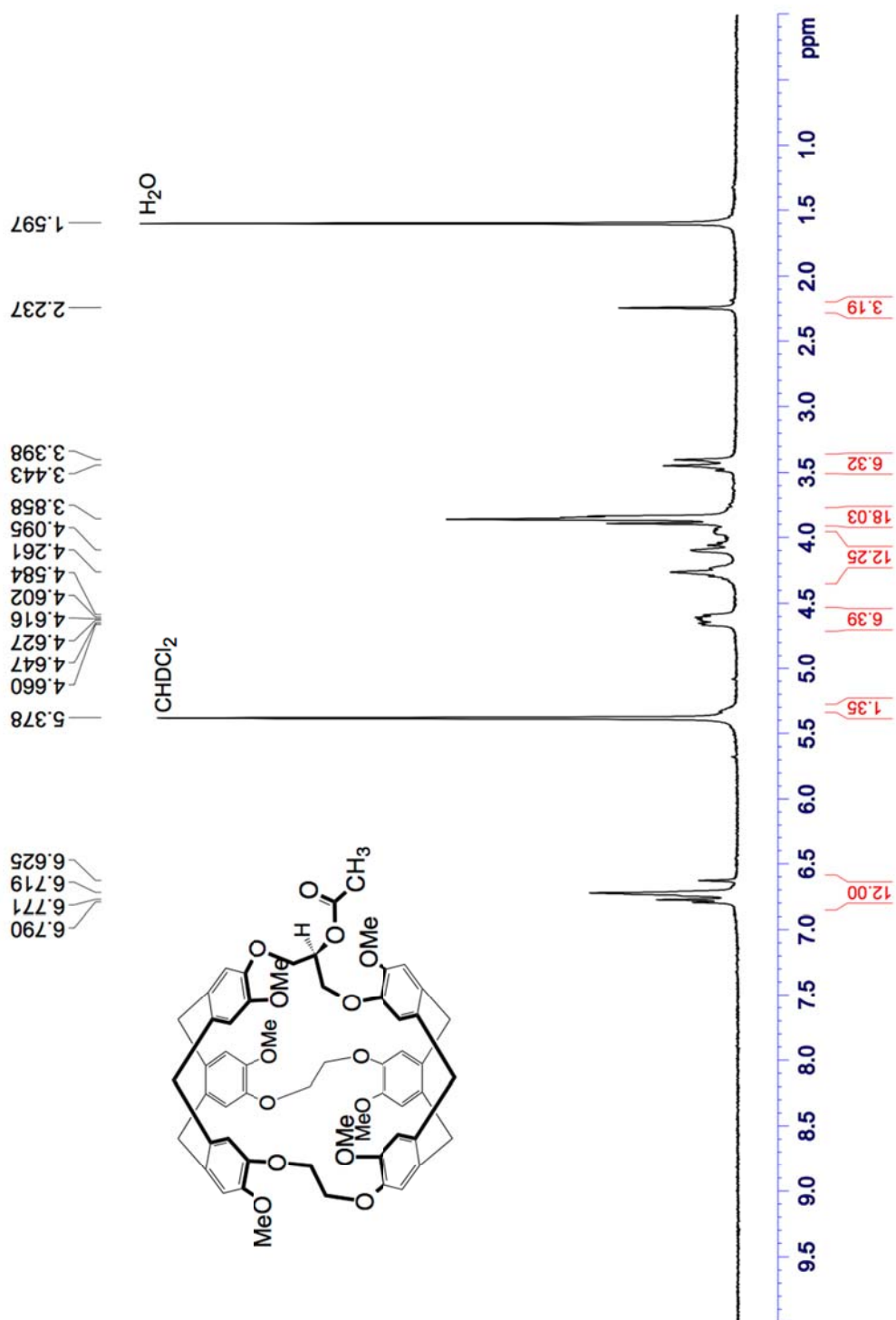


Figure S13: ¹H NMR spectrum (300 MHz) of (rac)-**2** recorded in CD₂Cl₂ at 25 °C.

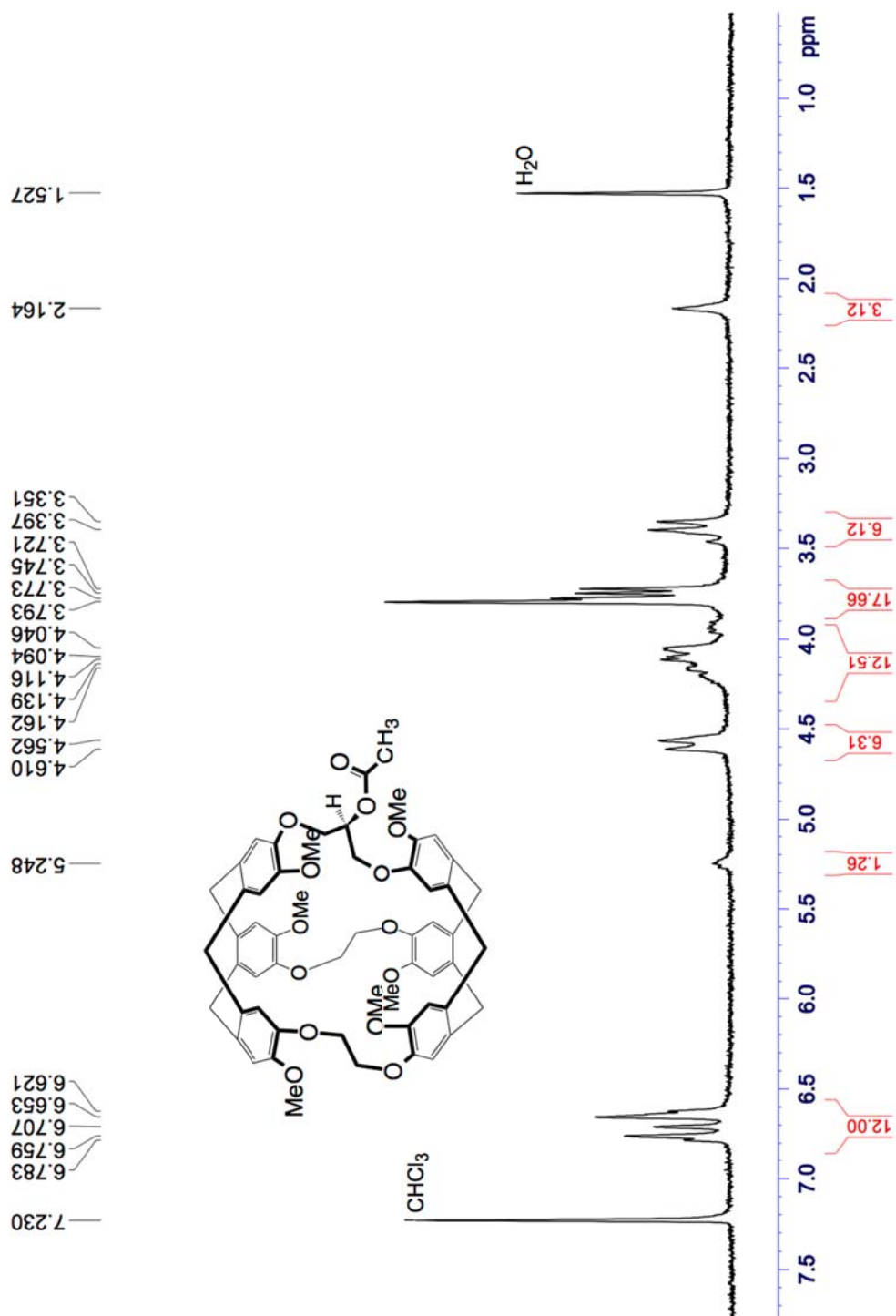


Figure S14: ^1H NMR spectrum (300 MHz) of (rac)-2 recorded in CDCl_3 at 25 °C.

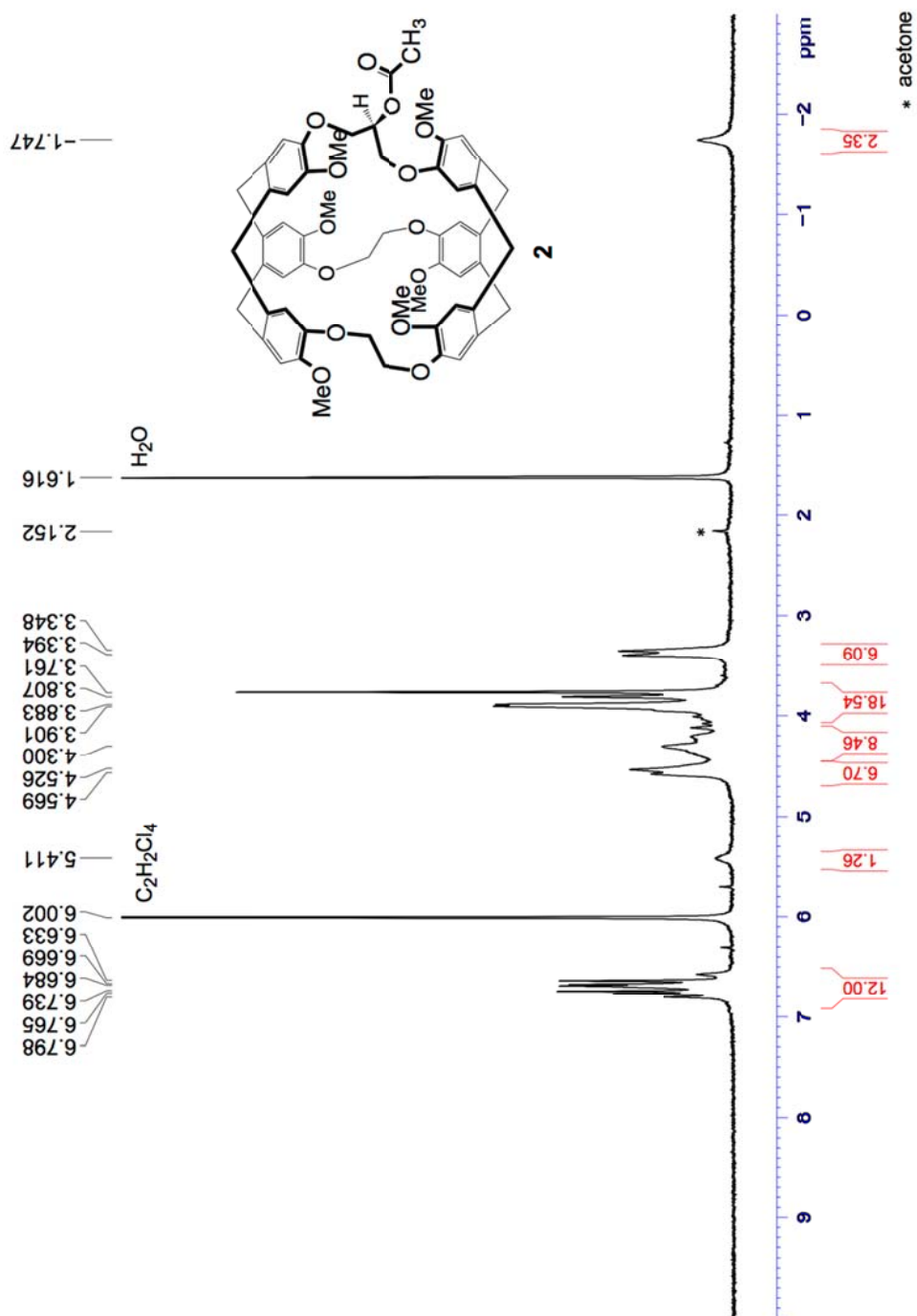


Figure S15: ^1H NMR spectrum (300 MHz) of (rac)-**2** recorded in 1,1,2,2-tetrachloroethane- d_2 at 25 °C.

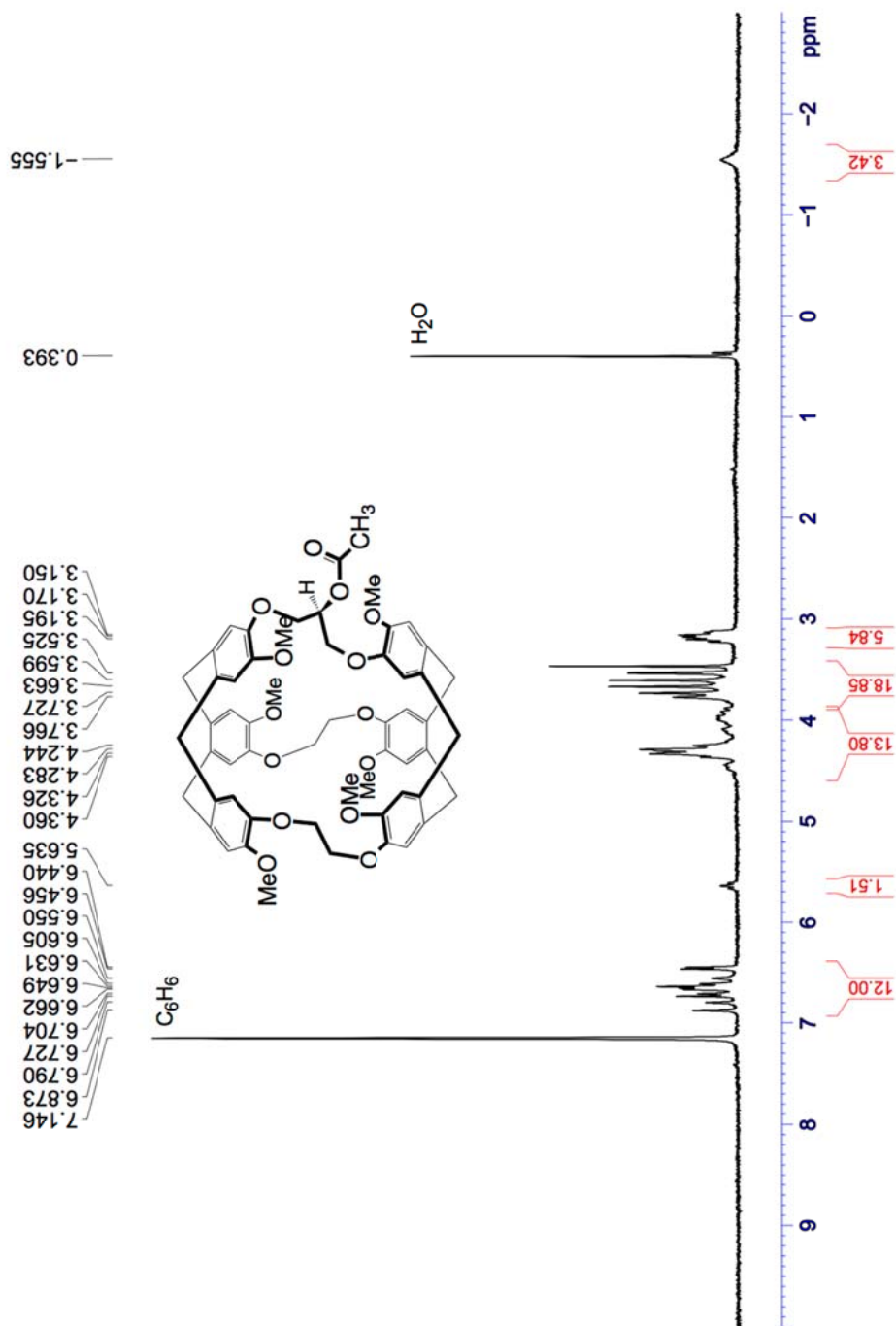


Figure S16: ¹H NMR spectrum (300 MHz) of (rac)-**2** recorded in benzene-*d*₆ at 25 °C.

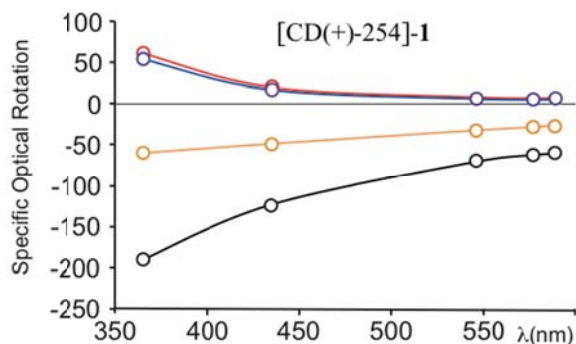


Figure S17: Specific Optical Rotation (SOR) values measured for [CD(+)₂₅₄]-**1** and [CD(-)₂₅₄]-**1** in CH₂Cl₂ (black), CHCl₃ (orange), DMSO (blue) and C₂H₂Cl₄ (red) at 25 °C. Plot of the SOR (10⁻¹ deg cm² g⁻¹) values versus λ (nm) for the [CD(+)₂₅₄]-**1** enantiomer.

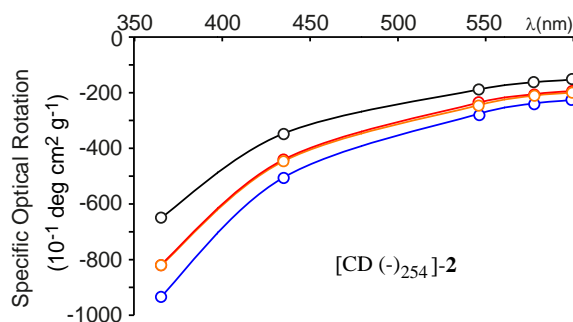


Figure S18: Specific Optical Rotation (SOR) values measured for [CD(+)₂₅₄]-**2** and [CD(-)₂₅₄]-**2** in CH₂Cl₂ (black), CHCl₃ (orange), DMSO (blue) and C₂H₂Cl₄ (red) at 25 °C. Plot of the SOR (10⁻¹ deg cm² g⁻¹) values versus λ (nm) for the [CD(+)₂₅₄]-**2** enantiomer.

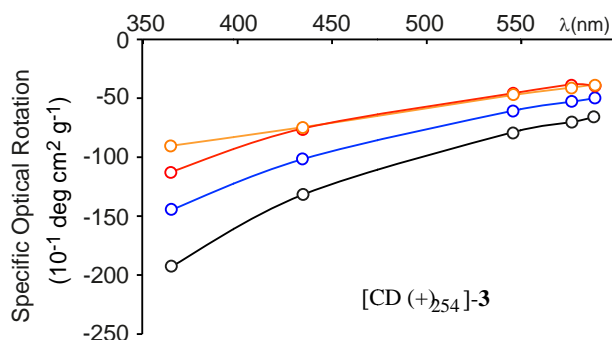


Figure S19: Specific Optical Rotation (SOR) values measured for [CD(+)₂₅₄]-**3** and [CD(-)₂₅₄]-**3** in CH₂Cl₂ (black), CHCl₃ (orange), DMSO (blue) and C₂H₂Cl₄ (red) at 25 °C. Plot of the SOR (10⁻¹ deg cm² g⁻¹) values versus λ (nm) for the [CD(+)₂₅₄]-**3** enantiomer.

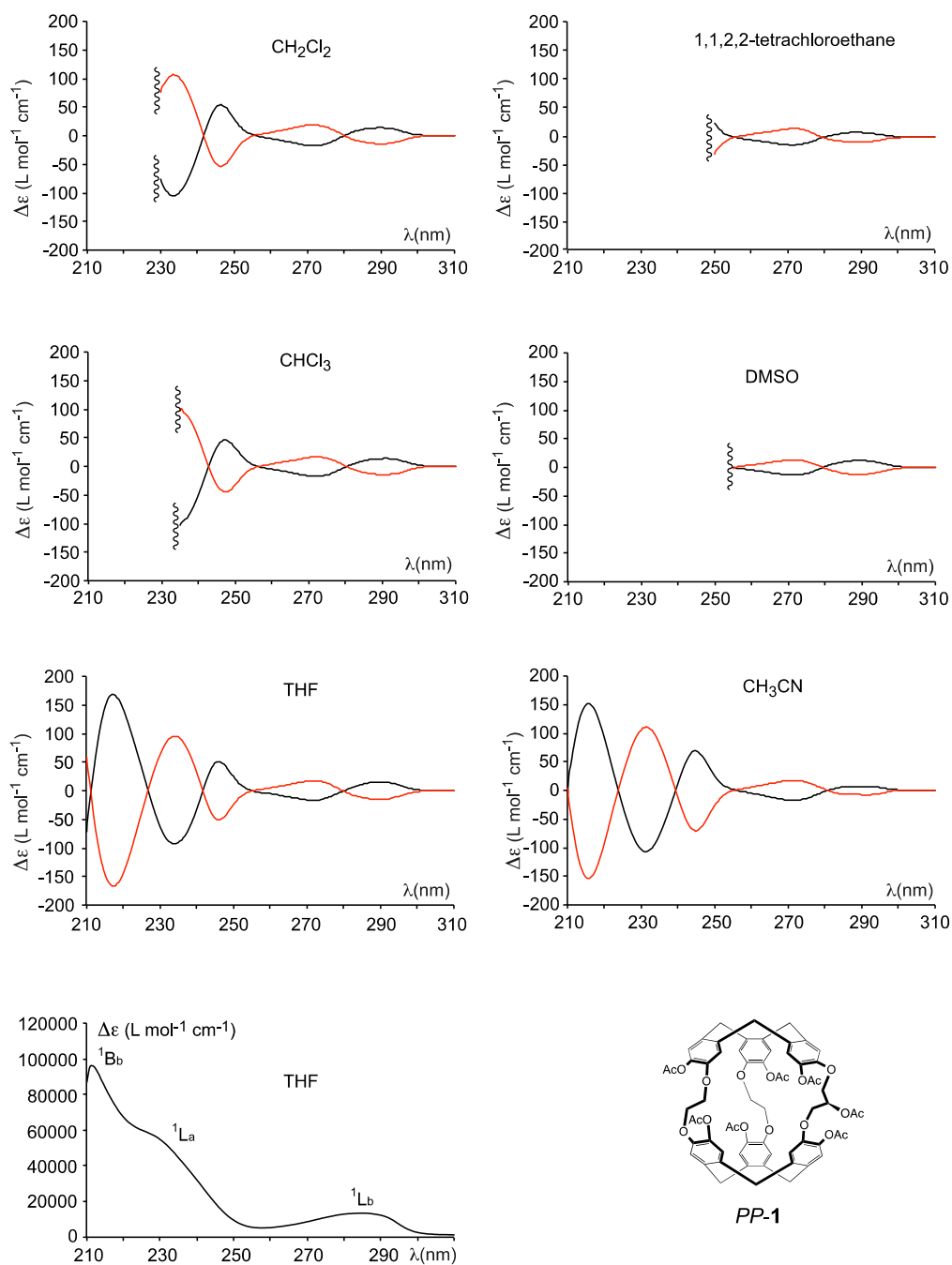


Figure S20: ECD spectra of [CD(+)₂₅₄]-**1** (black spectra) and [CD(-)₂₅₄]-**1** (red spectra) recorded in CH_2Cl_2 , CHCl_3 , THF, CH_3CN , DMSO and $\text{C}_2\text{H}_2\text{Cl}_4$ at 20 °C. ($c = 10^{-4} - 10^{-5}$ M). UV-visible spectrum of **1** recorded in THF at 25 °C ($c = 1.12 \cdot 10^{-5}$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

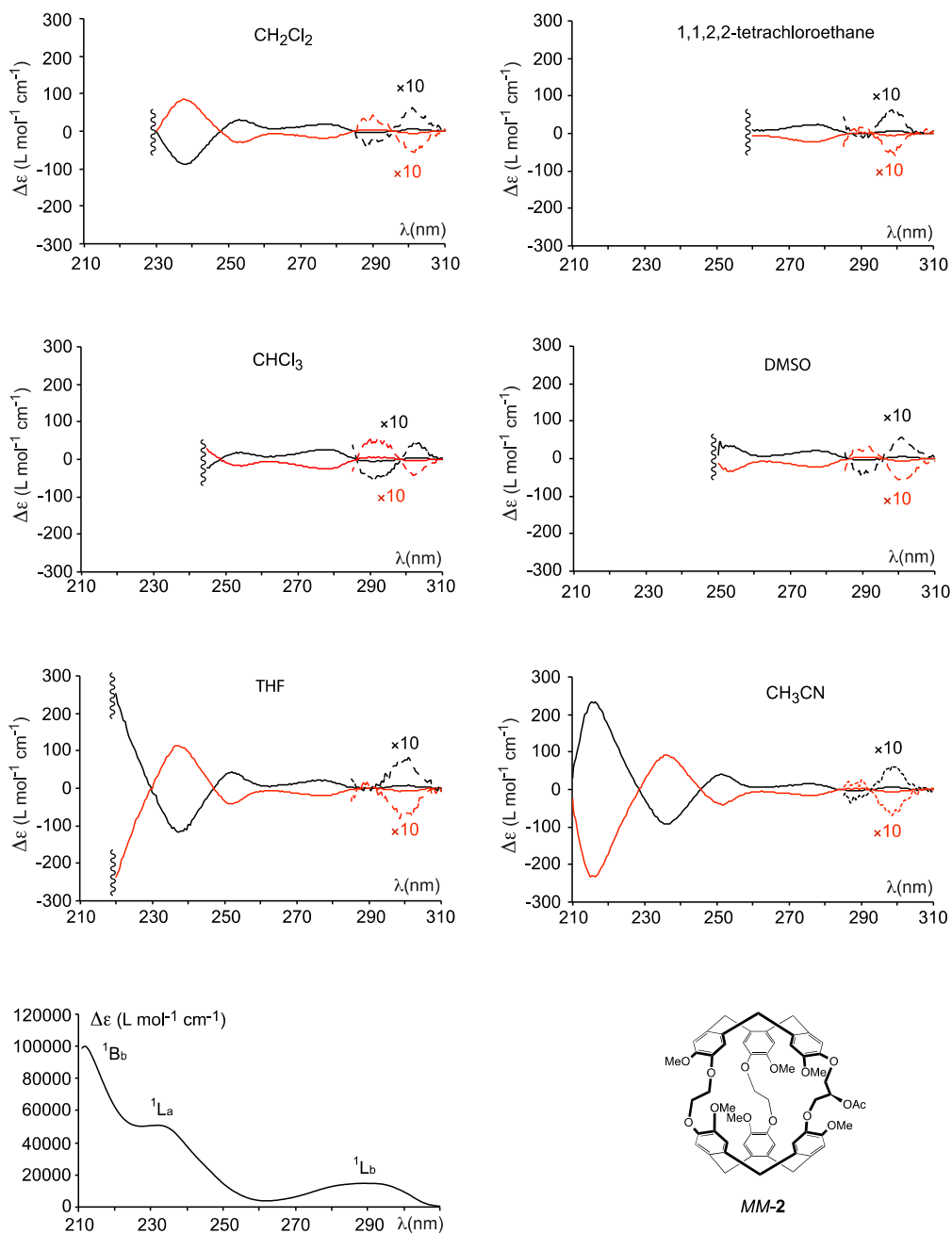


Figure S21: ECD spectra of [CD(+)₂₅₄]-**2** (black spectra) and [CD(-)₂₅₄]-**2** (red spectra) recorded in CH₂Cl₂, CHCl₃, THF, CH₃CN, DMSO and C₂H₂Cl₄ at 20 °C. (*c* = 10⁻⁴ – 10⁻⁵ M). UV-visible spectrum of **2** recorded in THF at 25 °C (*c* = 1.02 10⁻⁵ M).

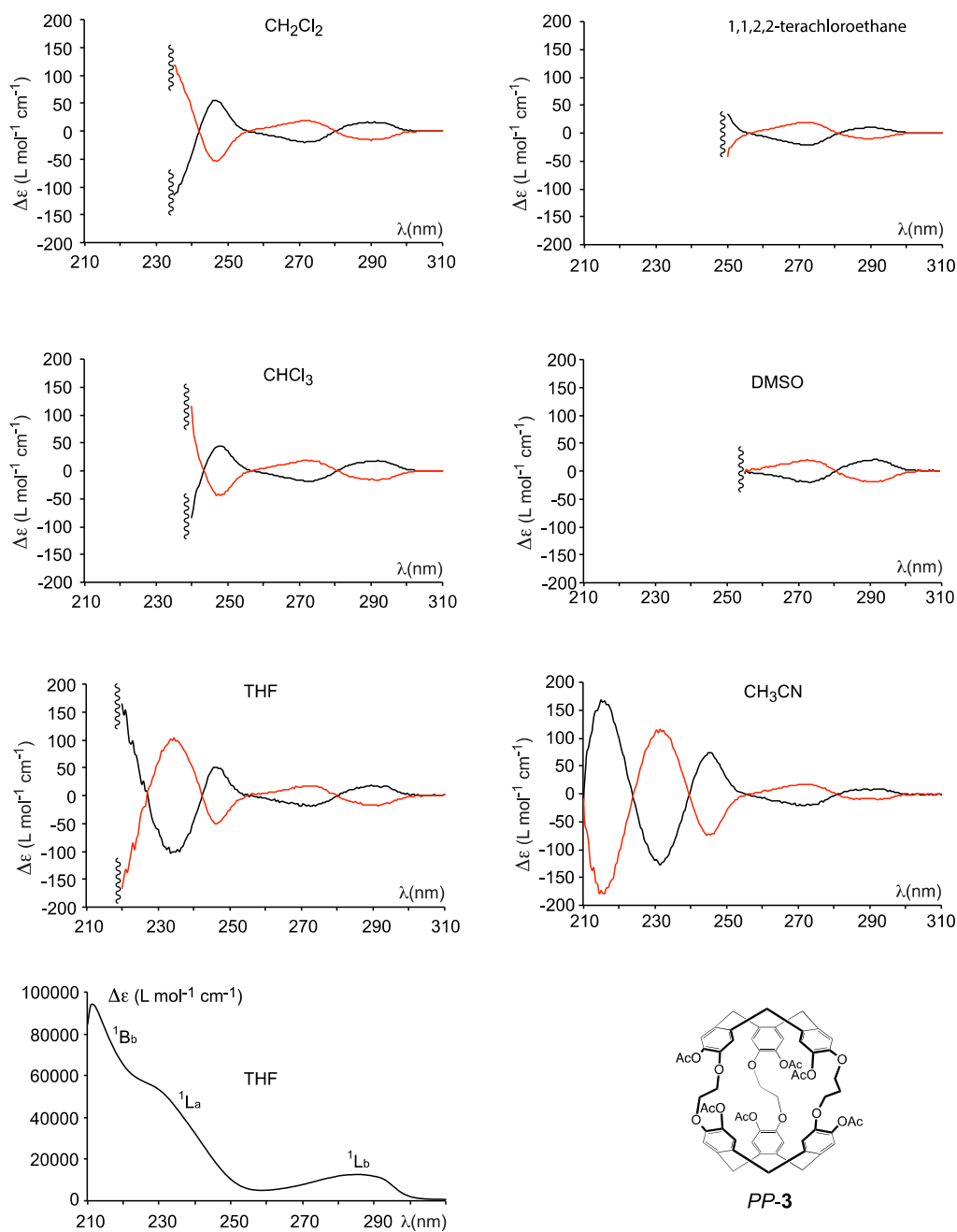


Figure S22: ECD spectra of [CD(+)₂₅₄]-**3** (black spectra) and [CD(-)₂₅₄]-**3** (red spectra) recorded in CH₂Cl₂, CHCl₃, THF, CH₃CN, DMSO and C₂H₂Cl₄ at 20 °C. (c = 10⁻⁴ – 10⁻⁵ M). UV-visible spectrum of **3** recorded in THF at 25 °C (c = 0.99 × 10⁻⁵ M).

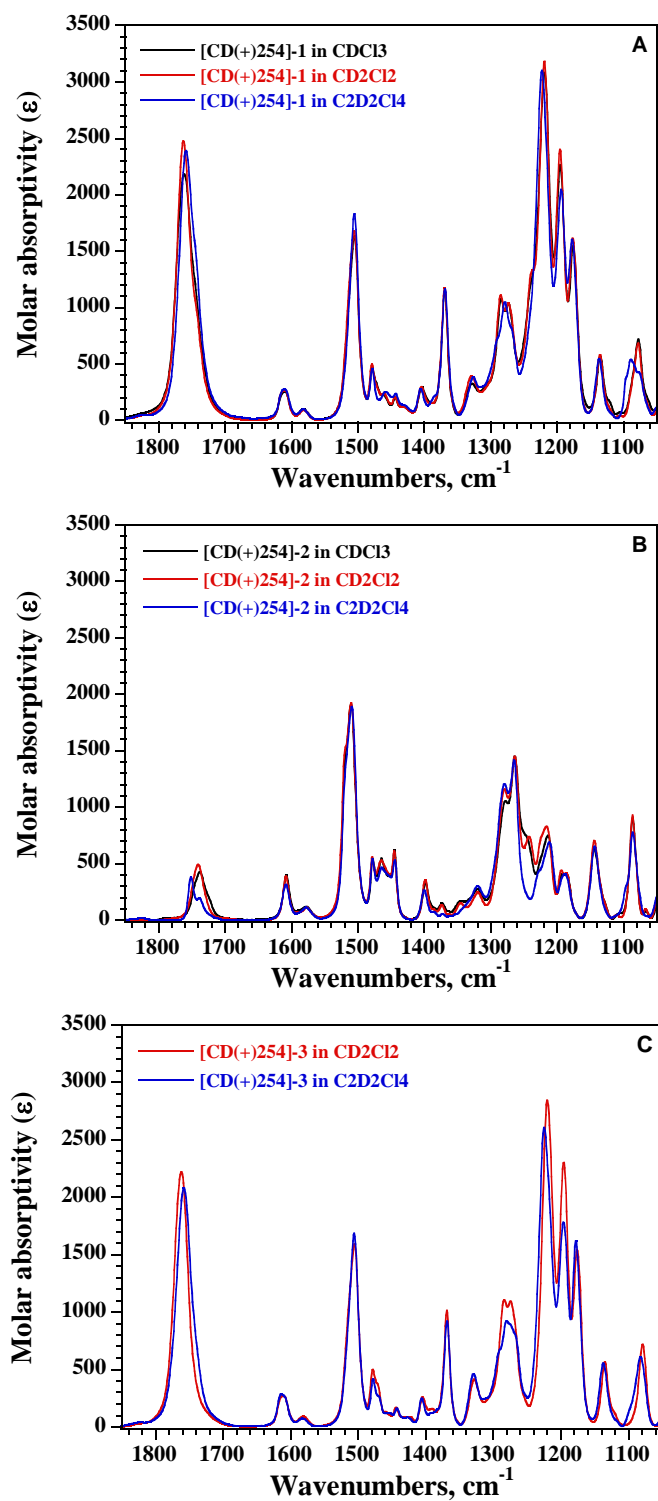


Figure S23: IR spectra of a) [CD(+)₂₅₄]-1, b) [CD(+)₂₅₄]-2 and [CD(+)₂₅₄]-3 c) in CDCl₃ (black spectra), CD₂Cl₂ (red spectra) and C₂D₂Cl₄ (blue spectra) solvents (0.015 mM, 250 μm path length).

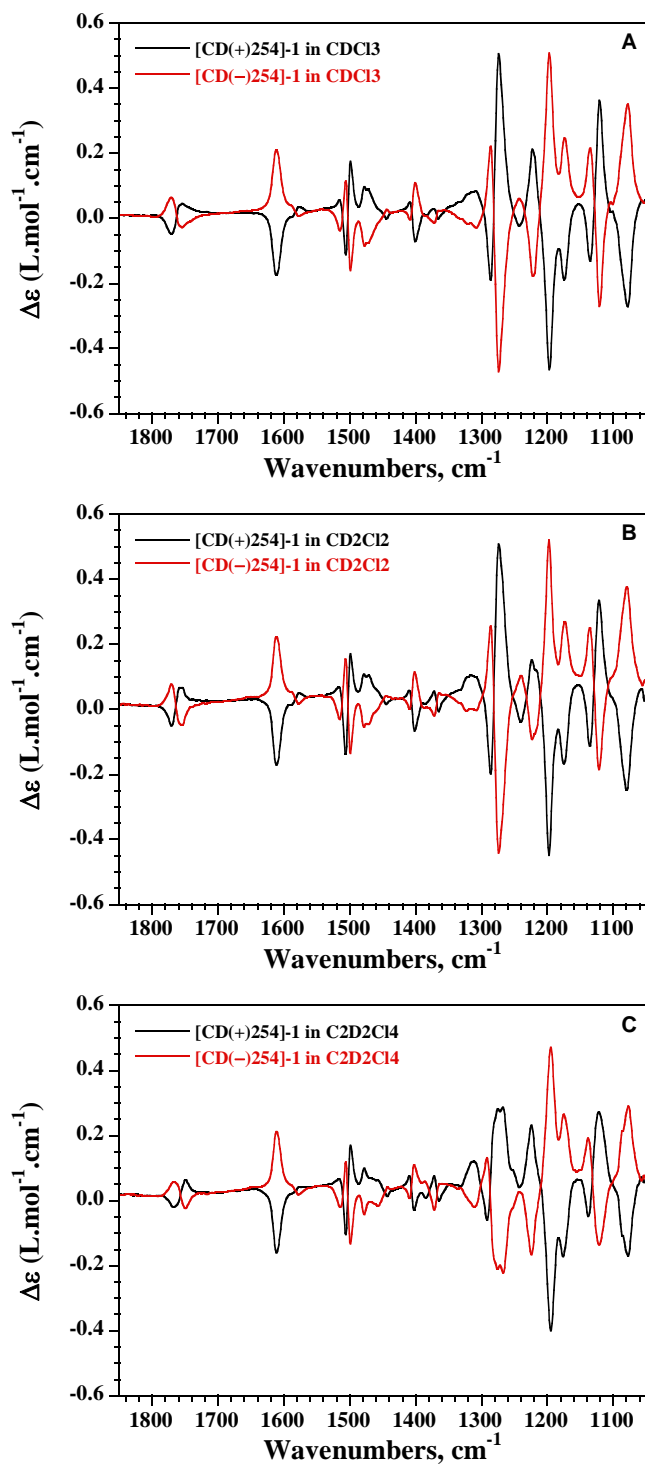


Figure S24: VCD spectra of $[\text{CD}(+)\text{254}]\text{-1}$ (black spectra) and $[\text{CD}(-)\text{254}]\text{-1}$ (red spectra) in a) CDCl_3 , b) CD_2Cl_2 , and c) $\text{C}_2\text{D}_2\text{Cl}_4$ solvents (0.015 mM, 250 μm path length).

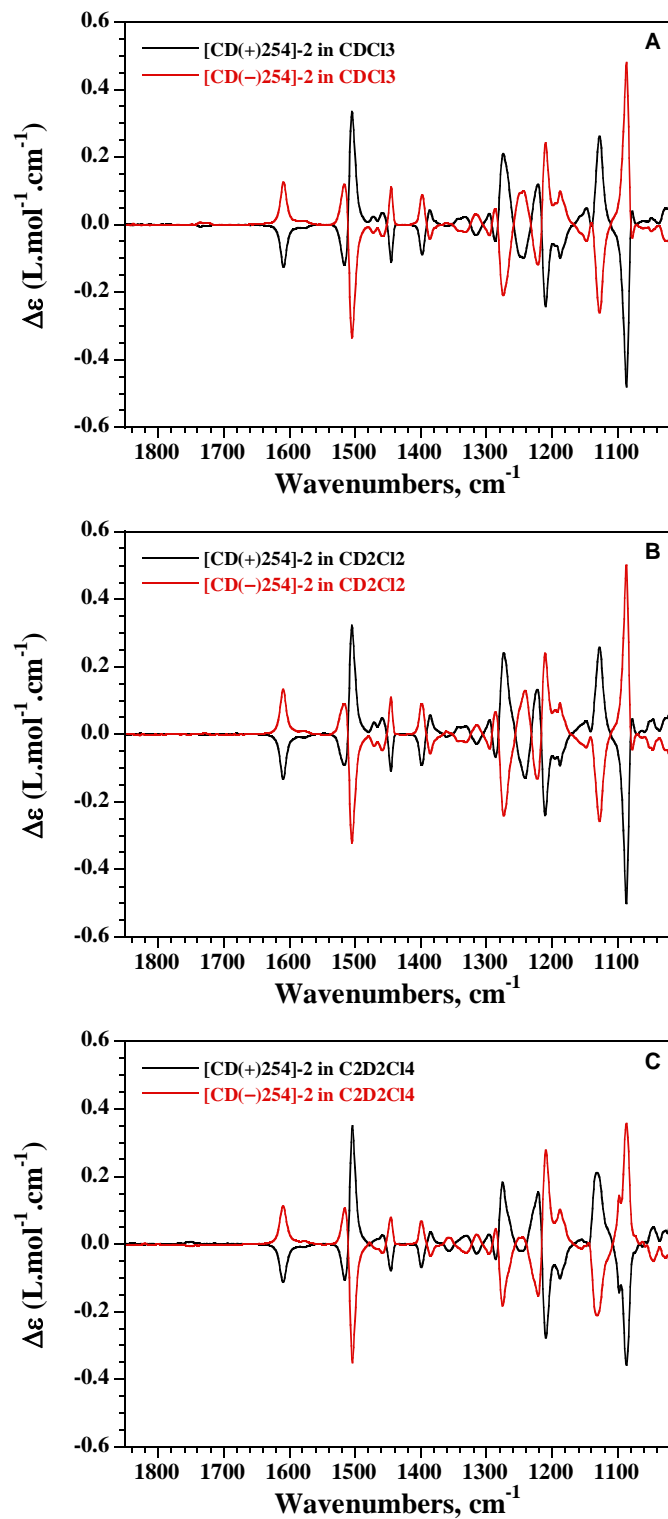


Figure S25: VCD spectra of $[\text{CD}(+)\text{-}254]\text{-}2$ (black spectra) and $[\text{CD}(-)\text{-}254]\text{-}2$ (red spectra) in a) CDCl_3 , b) CD_2Cl_2 , and c) $\text{C}_2\text{D}_2\text{Cl}_4$ solvents (0.015 mM, 250 μm path length).

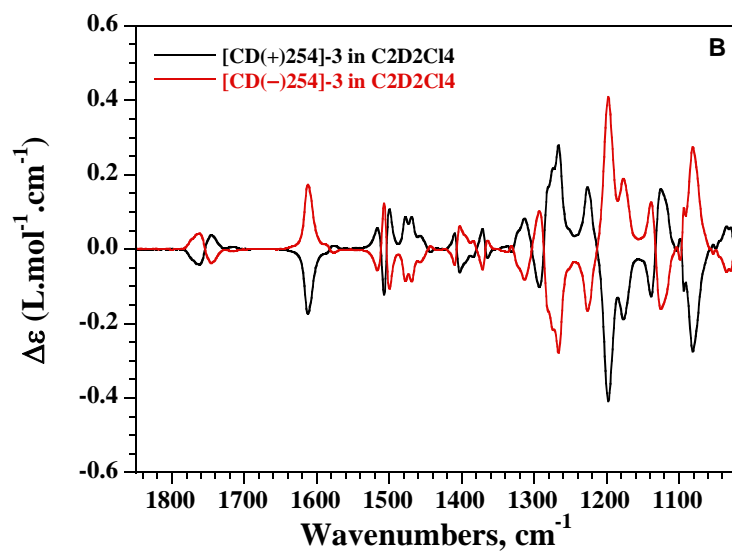
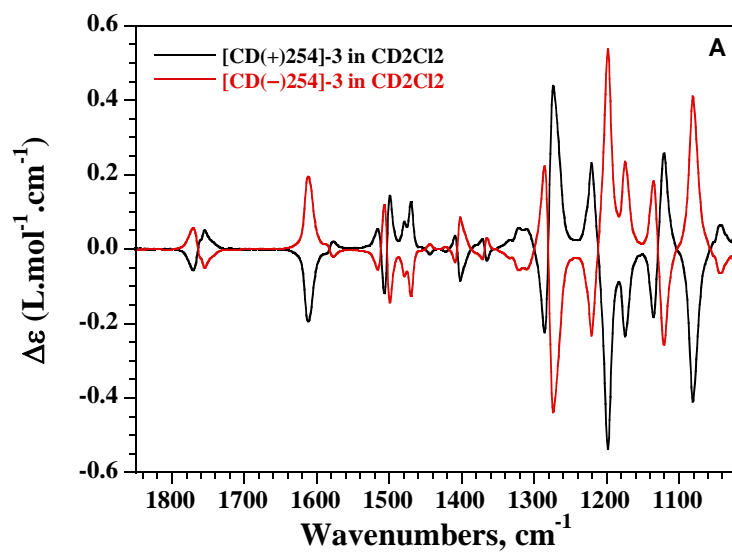
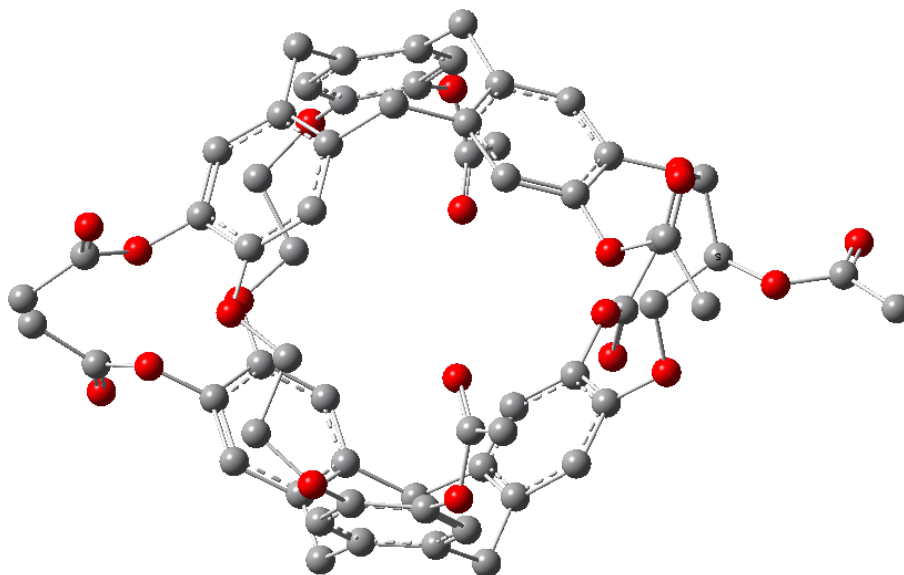


Figure S26: VCD spectra of [CD(+)₂₅₄]-**3** (black spectra) and [CD(-)₂₅₄]-**3** (red spectra) in a) CD₂Cl₂ and b) C₂D₂Cl₄ solvents (0.015 mM, 250 μ m path length).

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



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

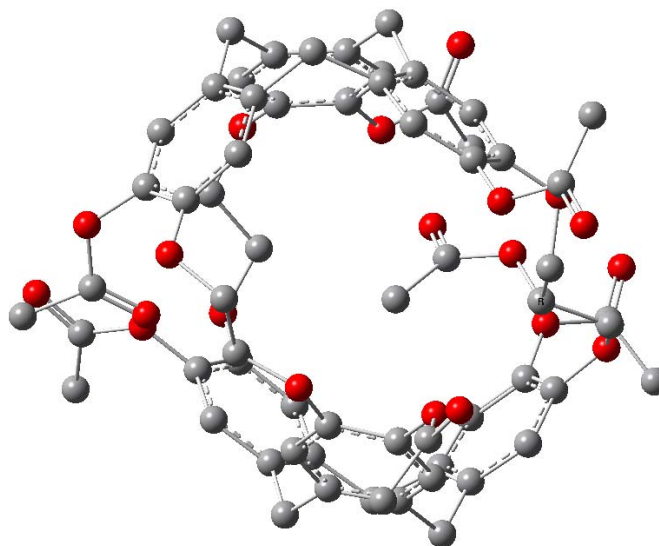
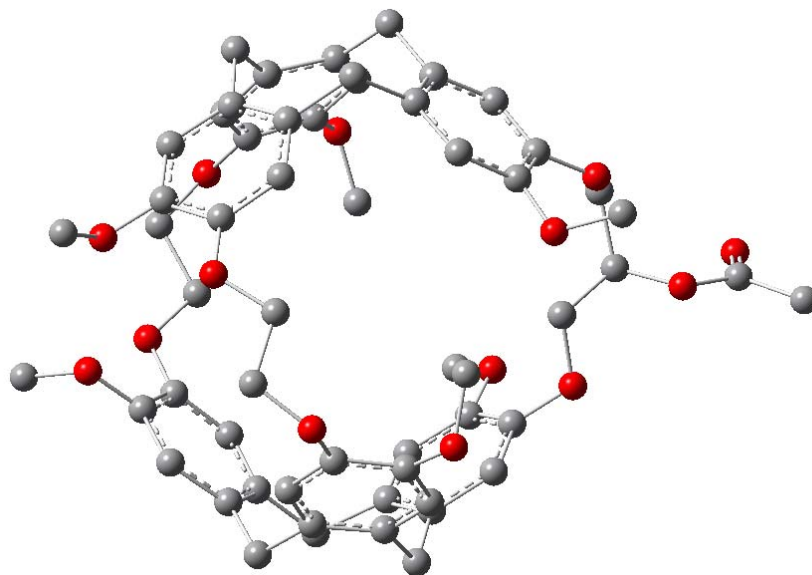


Figure S27: Optimized geometry of *PP-1* enantiomer calculated at the density functional theory (DFT) level using B3LYP functional and 6-31G** basis set with the use of IEFPCM model of solvent (IEFPCM = CH₂Cl₂ and C₂H₂Cl₄).

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



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

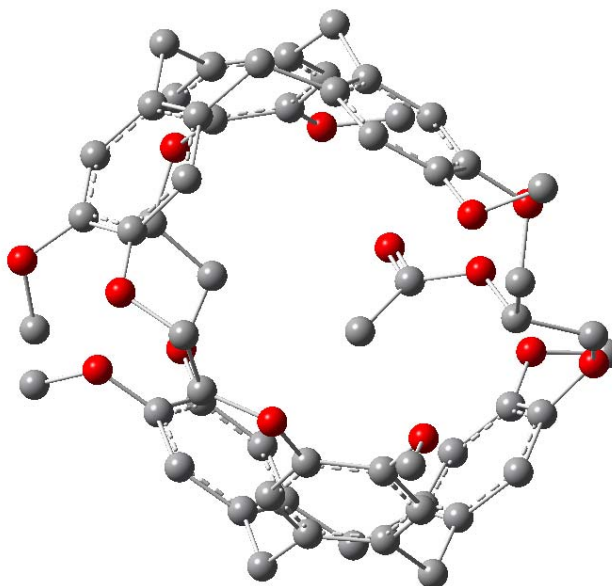


Figure S28: Optimized geometry of *MM-2* enantiomer calculated at the density functional theory (DFT) level using B3LYP functional and 6-31G** basis set with the use of IEFPCM model of solvent (IEFPCM = CH₂Cl₂ and C₂H₂Cl₄).

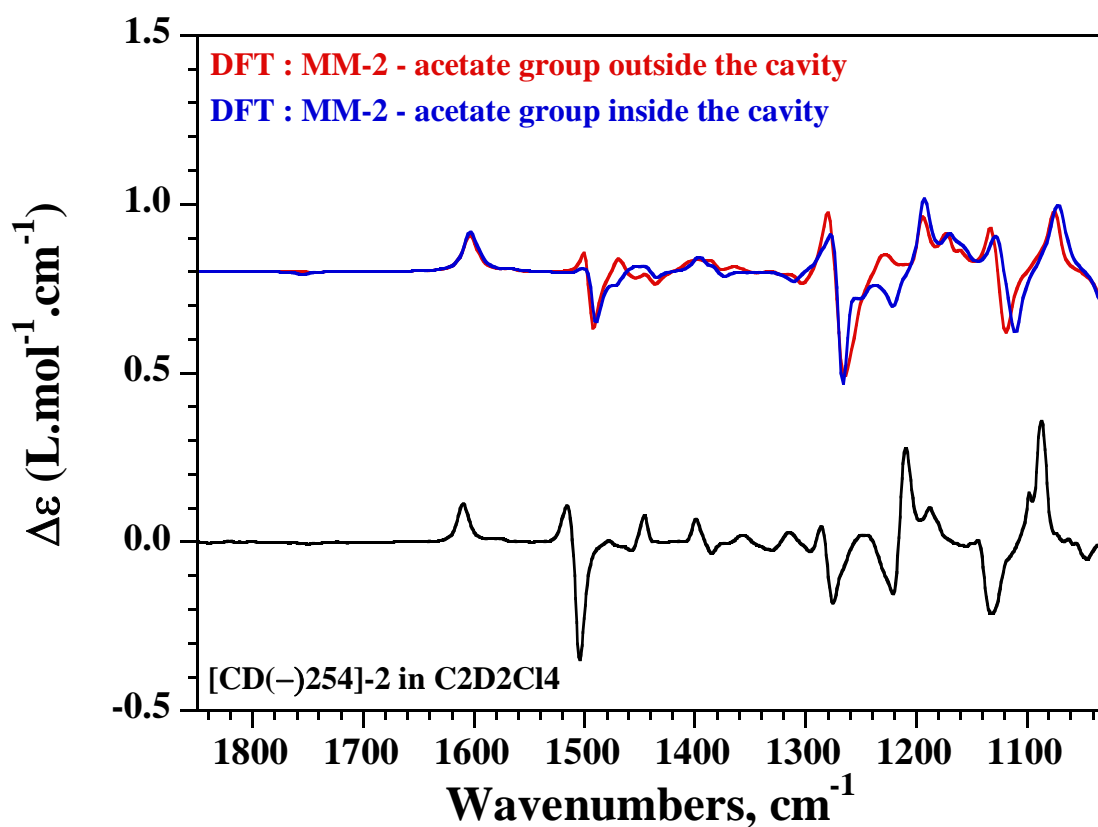


Figure S29: Comparison of experimental VCD spectrum of [CD(-)₂₅₄]-**2** in C₂D₂Cl₄ solution (15 mM, 250 μm path length) and VCD spectra of *MM-2* calculated at the B3LYP/6-31G** level (IEFPCM = C₂H₂Cl₄) for the *trans* and *gauche-gauche* conformations of the ethylenedioxy and propylenedioxy linkers, 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.

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

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