ENANTIOSELECTIVE HELICAL FOLDING INSIDE A SELF-ASSEMBLED, CYLINDRICAL CAPSULE

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ASSIGNMENT OF 1H NMR SPECTRA

The ^{1}H NMR and the 2D COSY spectra of the encapsulation complex of nanocapsule with *rac*-2-tetradecanol in mesitylene-d_{12} are depicted in Figure S1 and S2. As expected, the unsymmetrical guest gives rise to a more complex series of signals in the upfield region of the spectrum compared to the spectrum reported for tetradecane.[1] In addition, the hydrogens at C3, C4 and C5 are diastereotopic indicating that this part of the guest molecule is fixed in its helical conformation on the chemical shift time scale.

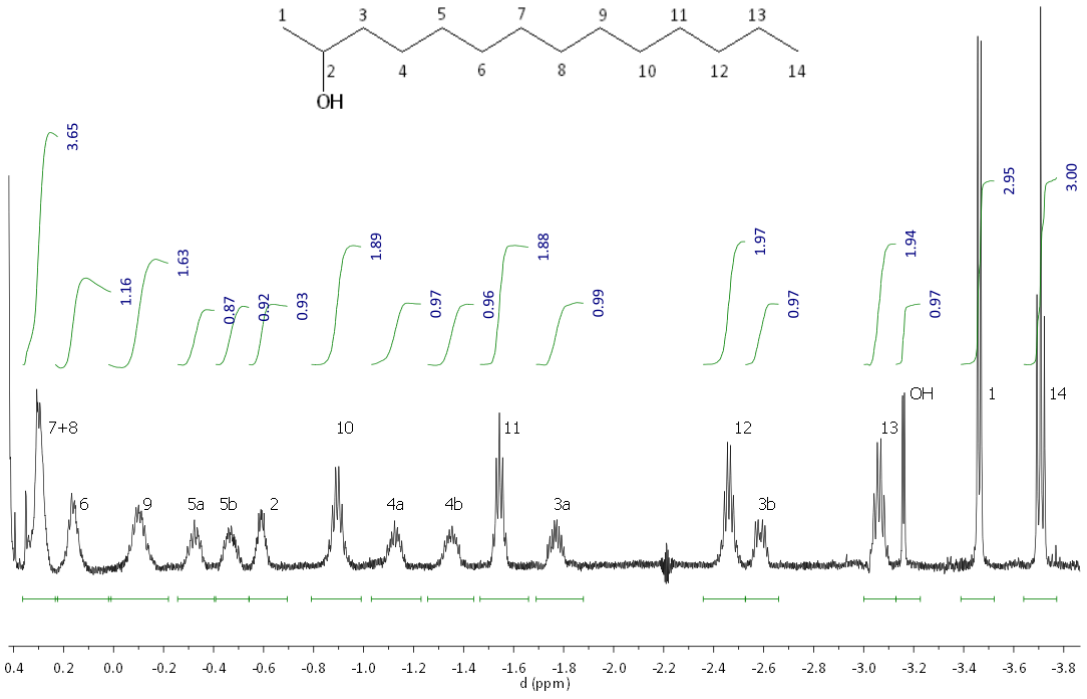


Figure S1. Upfield portion of the ^{1}H NMR spectrum at 400 MHz in mesitylene-d_{12} at 298 K of the encapsulation complex of capsule (2 mM) with *rac*-2-tetradecanol (100 mM).

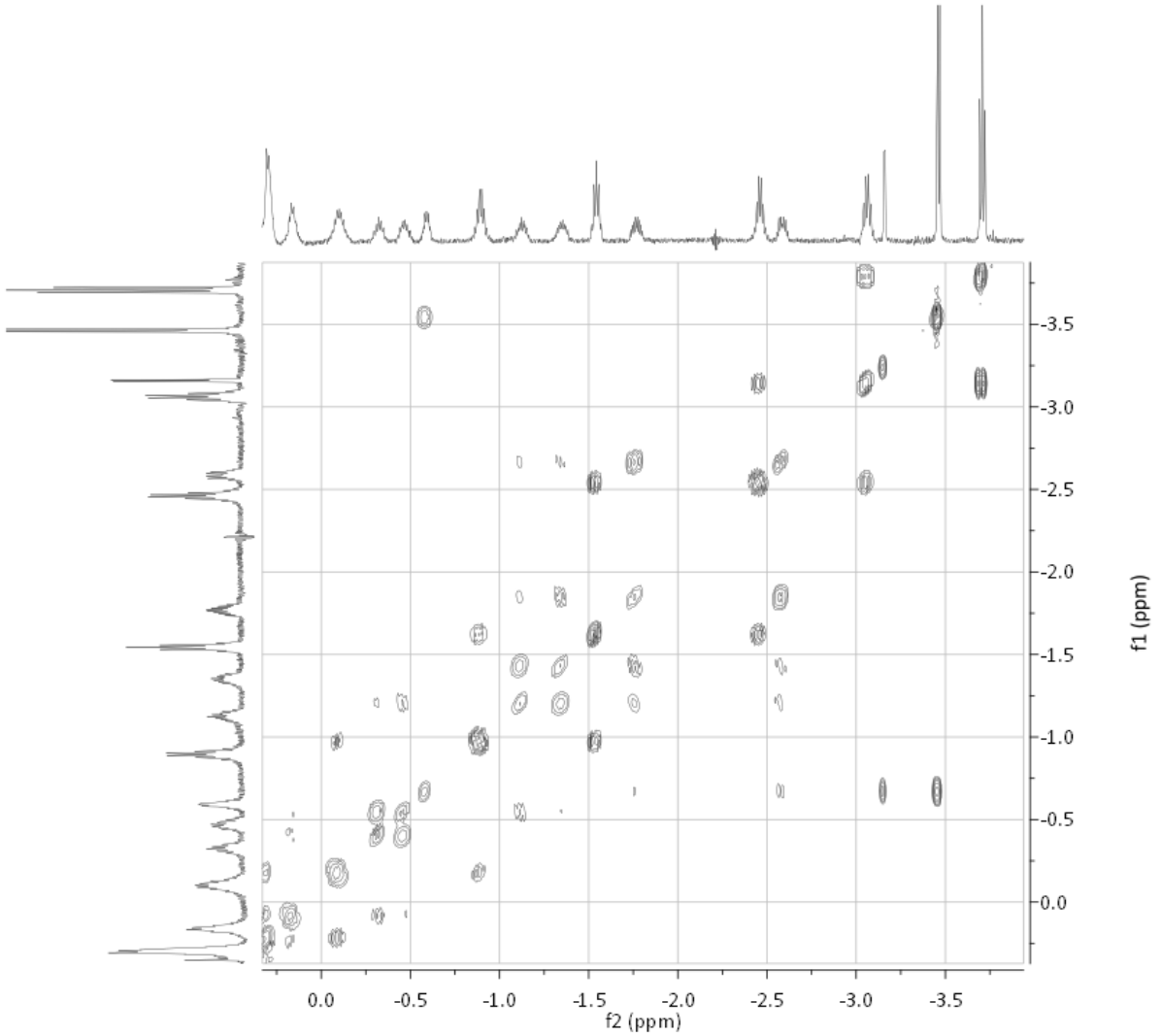


Figure S2. Upfield portion of the 2D COSY spectrum at 500 MHz in mesitylene-d_{12} at 298 K of the encapsulation complex of capsule (2 mM) with *rac*-2-tetradecanol (100 mM).

COMPETITIVE CIRCULAR DICHROISM EXPERIMENTS

Addition of undecane to a complex of capsule and enantiomerically enriched (*R*)-2-tetradecanol was performed in order to exclude "solvent" effects as origin for the found CD. Since the exchange in mesitylene as solvent is rather slow, the decay of the signal takes several days. After 2d, no more decrease of signal intensity is observed.

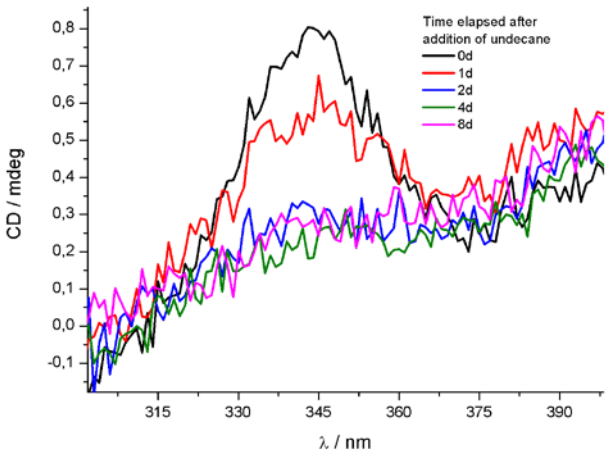


Figure S3. CD spectra of competitive complexation of n-undecane and (*R*)-2-tetradecanol in the self-assembled capsule.

EXPERIMENTAL SECTION

NMR. All spectra were recorded at 25°C on a Bruker DPX400 instrument (Analytische Messtechnik, Karlsruhe, Germany). Chemical shifts (δ) are reported in parts per million (ppm) relative to traces of partially deuterated solvent.

Preparation of NMR samples. [1] Solutions of encapsulation complexes were prepared by mixing 3.37 mg (1.00 µmol) of capsule dimer in 100 µL of mesitylene-d_{12} with 10.7 mg (50 µmol) in 400 µL solutions of *rac*-2-tetradecanol. Prior to usage, *rac*-2-tetradecanol was purified by column chromatography (cyclohexane/ EtOAc 7:1).

Preparation of samples. A capsule stock suspension was prepared from 1.35 mg (0.400 µmol) of capsule in 0.400 ml mesitylene. In a typical experiment, 4.30 mg (20.1 µmol) of *rac*-2-tetradecanol (or enantiomer enriched (*S*)- or (*R*)-2-tetradecanol) in 0.180 ml mesitylene was added to 0.020 ml of the capsule stock suspension. The resulting mixture of 2-tetradecanol (100 mM) and capsule (0.100 mM) in mesitylene was transferred to a quartz cell (1 mm) and CD spectra were recorded (JASCO, J-810 spectropolarimeter) when equilibriums had been reached (typically within 3-5 days).

Competitive CD experiment. A sample was prepared with (*R*)-2-tetradecanol (90% *ee*) as described above. After 5 days a CD spectrum was recorded and then 8.48 µL (6.28 mg, 40.2 µmol) of *n*-undecane was added to the sample. A CD spectrum of the sample mixture was recorded immediately after addition of *n*-undecane and again with 24 hours intervals until equilibrium had been reached.

Preparation of compounds: Kinetic resolution of *rac*-2-tetradecanol was achieved using Amano Lipase PS as previously reported by Othani *et al.*[2]

Scheme S1. Kinetic resolution of *rac*-2-tetradecanol using Amano Lipase PS. Synthetic route to (*R*)- 2-tetradecanol

Acetic acid 1-methyl tridecyl ester (3a) was prepared using the procedure reported by Tsubuki *et al*.[3] Under an atmosphere of argon, 0.500 g (2.33 mmol) of 2-tetradecanol and 0.661 μL (0.714 g, 6.99 mmol) of acetic acid anhydride were dissolved in 15 ml dichloromethane. The solution was cooled to 0 °C and 0.754 μL (0.737 g, 9.32 mmol) of pyridine and 28.5 mg (0.233 mmol) of *N,N*-dimethylamino pyridine were added. The reaction mixture was stirred at 0 °C for 1 hour and then quenched by addition of 50.0 g of crushed ice. The product was extracted with 3 × 25 ml of *t*-butyl methyl ether and the combined organic phases were dried over magnesium sulfate. The solvent was removed by evaporation under reduced pressure. The crude product was purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 9:1) providing the title product as clear oil (0.560 g, 94%). R_f (cyclohexane/ethyl acetate 5:1) = 0.67. GC (HP 5, method : 25 min) R_t = 13.76 min (100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, ^3J = 6.7 Hz, CH_3), 1.20 (d, 3 H, ^3J = 6.3 Hz, CH_3), 1.25 (bs, 20 H, CH_2), 1.42–1.59 (m, 2 H, CH), 2.02 (s, 3 H, OAc), 4.84–4.92 (m, 1 H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 20.0, 21.4, 22.7, 25.4, 26.9, 29.3, 29.46, 29.53, 29.57, 29.6, 29.7, 31.9, 35.9, 71.8, 170.8. MS (EI): *m/z* (%) = 256 (2, M^+), 196 (48), 125 (12), 111 (26), 97 (42), 87 (100), 83 (38), 69 (36), 55 (36). HR-EIMS ($C_{16}H_{32}O_2$): calcd. 256.2402, found 241.2171 ($M^+ - CH_3$).

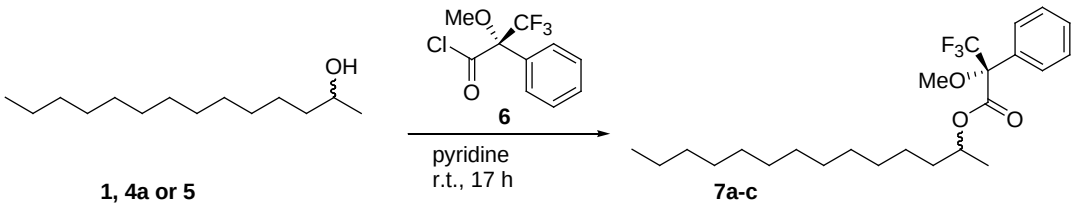
(*R*)-2-Tetradecanol (4a) was obtained using the procedure reported by Ohtani *et al.*[4] Under an atmosphere of argon, 0.375 g (1.46 mmol) of acetic acid 1-methyl-tridecyl ester (**3a**) and 0.400 g of Amano Lipase PS (≥ 30.000 U/g, Aldrich) were dissolved/suspended in 6 ml of acetone and 9 ml of 0.1 M phosphate buffer (pK = 8.5). The mixture was stirred at room temperature for 17 hours and then filtrated over a short path of Celite (cake was washed with *t*-butyl methyl ether). The products were extracted with 3 × 10 ml of *t*-butyl methyl ether and the combined organic phases were washed with 15 ml brine and dried over magnesium sulfate. The solvents were removed by evaporation under reduced pressure and the products were purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 9:1) providing 0.255 g (68%) of enantiomeric enriched acetic acid 1-methyl-tridecyl ester (**3a**) and 69.0 mg (22%) of (*R*)-2-tetradecanol (**4**) as a colorless solid. R_f (cyclohexane/ethyl acetate 5:1) = 0.31. GC (HP 5, method: 25 min) R_t = 12.34 min (100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, ^3J = 6.9 Hz, CH_3), 1.18 (d, 3 H, ^3J = 6.2 Hz, CH_3), 1.26–1.33 (m, 20 H, CH_2), 1.39–1.48 (m, 2 H, CH_2), 3.75–3.82 (m, 1 H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 23.5, 25.8, 29.4, 29.64, 29.66, 29.68, 29.69 (2 × CH_2), 29.7, 32.0, 39.4, 68.2. MS (EI): *m/z* (%) = 213 (4, $M^+ - H$), 199 (20), 196 (40), 168 (24), 154 (12), 140 (10), 125

(23), 111 (44), 97 (84), 83 (83), 69 (84), 57 (100). HR-EIMS ($C_{14}H_{30}O$): calcd. 214.2297, found 199.2065 ($M^+ - CH_3$).

Scheme S2. Kinetic resolution of *rac*-2-tetradecanol using Amano Lipase PS. Synthetic route to (S)- 2-tetradecanol.

(*S*)-2-Tetradecanol (5): Ester **3b** (recovered from the partial hydrolysis towards the alcohol **4a**) was treated once more with Amano Lipase PS and the enantiomerically enriched ester **3c** was subjected to hydrolysis with potassium hydroxide as described in the following: Under an atmosphere of argon, 0.197 g (0.769 mmol) of ester 3c was dissolved in 5 ml of dioxane and 4 ml of aqueous KOH (50% w/v) was added to the solution. The reaction mixture was stirred under reflux conditions for 17 hours. At room temperature 10 ml of water was added to the reaction mixture and the product was extracted with 3 × 10 ml of *t*-butyl methyl ether. The combined organic phases were dried over magnesium sulfate and the solvent was removed by evaporation under reduced pressure. Purification by column chromatography (silica gel 60, cyclohexane/ethyl acetate 7:1) gave 108 mg (66%) of alcohol **5** as a colorless solid. ^{1}H, ^{13}C NMR chemical shifts and MS data were identical to those found for (*R*)-2-tetradecanol (4a).

Determination of diastereomeric excess



Scheme S3. Modification by Mosher's ester.

General procedure for the synthesis of Mosher's esters from alcohols 1, 4a and 5; Under an atmosphere of argon, 0.500 mmol of 2-tetradecanol and 0.600 mmol of (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride were added to 1.00 ml of dry pyridine. The mixture was stirred at room temperature for 17 hours, after which the reaction was quenched by addition of 5 ml water. The product was extracted with 3 × 10 ml of *t*-butyl methyl ether and the combined organic phases were washed with 2 × 5 ml of 1 M aqueous hydrochloric

acid, 10 ml of aqueous sodium carbonate (sat.) and 10 ml of brine. The organic phase was dried over magnesium sulfate and the solvent was removed by evaporation under reduced pressure. In all cases TLC indicated full conversion; R_f (cyclohexane/ethyl acetate 9:1) = 0.61.

NMR samples were prepared from crude products and the diastereomeric excess was determined by integration of ^{19}F NMR signals:

From *rac*-2-tetradecanol (1); ^{19}F NMR (300 MHz, $CDCl_3$): δ = –71.90 (s, (*R,S*), integral = 1.00), –71.96 (s, (*S,S*), integral = 1.00).

From (*R*)-2-tetradecanol (4a); ^{19}F NMR (300 MHz, $CDCl_3$): δ = –71.90 (s, (*R,S*), integral = 1.00), –71.96 (s, (*S,S*), integral = 0.05). *ee* = (1.00/1.05) – (0.05/1.05) * 100% = 90%.

From (*S*)-2-tetradecanol (5); ^{19}F NMR (300 MHz, $CDCl_3$): δ = –71.90 (s, (*R,S*), integral = 1.00), –71.96 (s, (*S,S*), integral = 4.72). *ee* = (4.72/5.72) – (1.00/5.72) * 100% = 66%.

CONFORMATIONAL ANALYSIS (FORCE FIELD)

Conformational analysis of the tetradecanol was performed using MacroModel 7.1 using the AMBER* force field. Figure S4 depicts the best 20 conformers of 1000 investigated structures found inside the capsule after superposition of the lower capsule half. The capsule as well as aliphatic protons were omitted for clarity. Only very few conformers adopt a significantly different orientation of the lower (chiral) part, which induces a helical shape in this lower end. However, in our investigations the upper part is significantly less ordered. Furthermore, the upper half is situated closer to the central axis of the capsule.

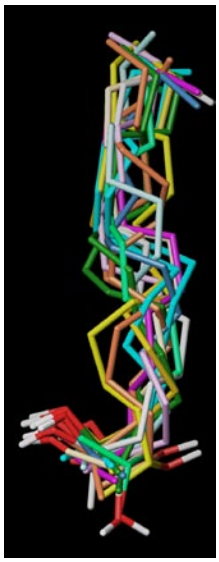


Figure S4. Tetradecanol after binding inside the capsule. Conformational analysis using force field methods. (overlay of 20 lowest energy conformers)

COMPUTATIONAL DETAILS AND FURTHER DISCUSSION

For CD calculation, the molecular dynamics simulations were performed with the DFTB+ package[5] on the SCC-DFTB-D level of theory. The simulation had a total runtime of 5 ps with a time step of 1 fs. The temperature was set to 500 K in the Andersen thermostat. A snapshot of the structure was taken every 50 steps and the CD spectrum from each snapshot was calculated using the PPP program.[6] It was found in structure optimizations that the capsule itself adopts a (slightly) twisted (chiral) conformation even without a guest. In consequence the two configurations of the alcohol group (*R, P*), the two configurations of the alkane (*M, P*) and two configurations of the capsule (denoted *A* and *B,* respectively) had to be considered (e.g. *RMA, RMB, SMA, SMB, RPA* etc.). The MD was performed for all eight possible

combinations of configurations. The CD spectra for a given alcohol-alkane combination (*RMA, RMB*) are then averaged to a single spectrum (denoted e.g. *R-M*).

The structures of each of the eight combinations were optimized with B97-D/SVP[7] and subsequent single point calculations were done with B97-D/TZVP using the TURBOMOLE suite of programs.[8,9] The resolution of identity (density fitting) for the Coulomb integral has been used:[10,11,12] The relative energies (ΔE) for each combination are given in table S1. The combination RMA is used as a reference and is set to zero. The combinations RMA/RMB (SMA/SMB) and the combination SPA/SPB (RPA/RPB) should give the same energy as they are enantiomers. The relative energy of 0.2 kcal/mol for the combination RMB is the result of the optimization procedure which converged to a close lying local minimum. The energy difference between the diastereoisomers (e.g. RMA and SMA) is 2.8 kcal/mol.

The helix configuration of the guest is well defined in the force-field and SCC-DFTB-D treatment. However, after the DFT-D optimization of the SCC-DFTB-D structures the helix is more deformed (mainly compressed at the ends) than initially and the configuration is not well defined anymore. The DFT-D and SCC-DFTB-D structures remain similar enough to safely allow for a calculation of the relative energies of the combinations with DFT-D.

The computed TD-PPP spectra are given below in a greater resolution.

Table S 1: Relative energies in kcal/mol for the eight combination of the configurations of the alcohol group (*S*,*R*), the folded alkane (*M*,*P*) and the capsule (A,B) .

combination	RMA	RMB	SMA	SMB	RPA	RPB	SPA	SPB
ΔE	0.0	0.2[a]	2.8	2.8	2.8	2.8	0.0	0.0

[a] Artifact of the optimization procedure

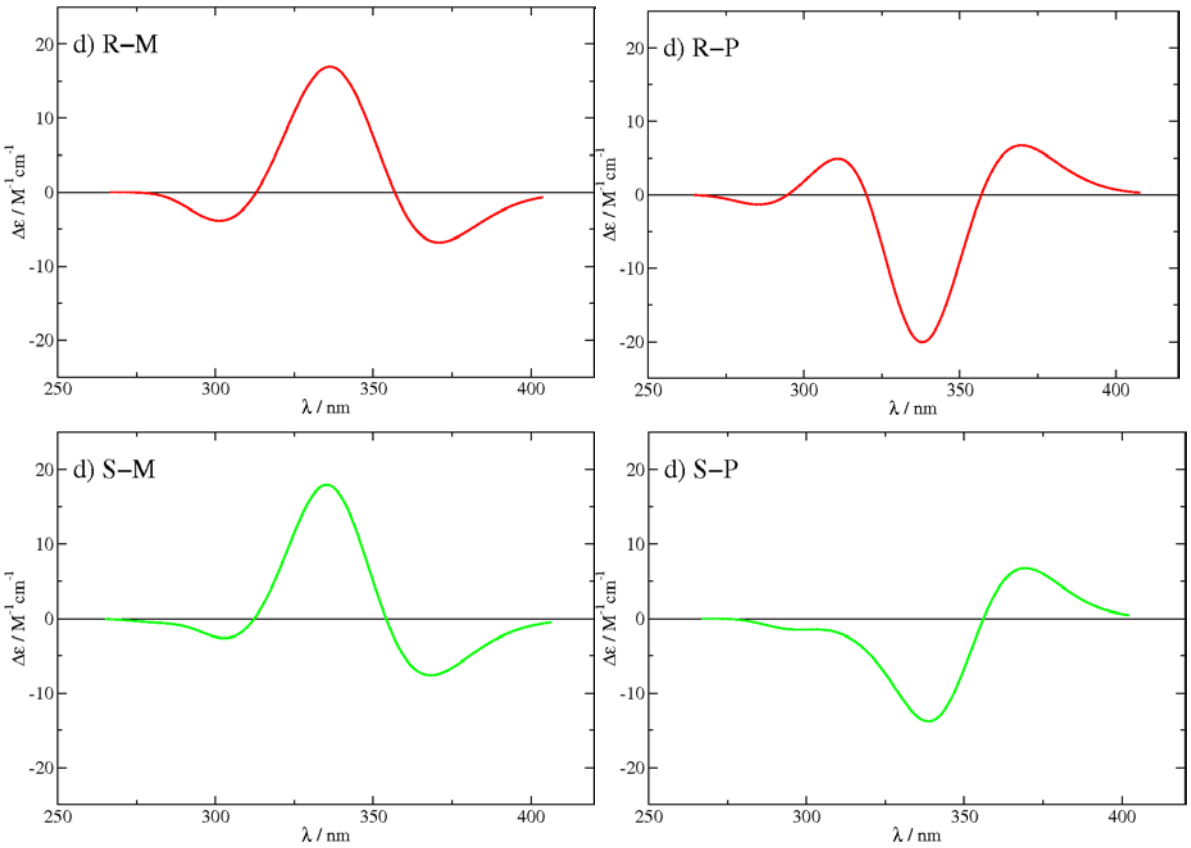


Figure S5. Calculated CD spectra (as depicted in the manuscript) in higher resolution. The first stereo descriptor (R/S) refers to the chiral center at C2 of the alcohol. The second (M/P) refers to the helical folding of the alkyl chain. Obviously, the folding of the chain dominates the sign of the Cotton effect at 330 nm.

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