Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

The Long-Awaited Synthesis and Self-Assembly of a Small Rigid C_3 Symmetric Trilactam

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1. General procedures

Reagents and solvents: Diethyl 2-oxopentanedioate was synthesized and purified following a reported procedure.[1] Ethyl 2-oxoacetate was purchased from Alfa Aesar as a technical solution (ca 50 wt. %) in toluene. The exact molar concentration of 2-oxoacetate was determined prior to use by ^{1}H NMR with dimethyl sulfone as the internal standard. *tert*-Butoxy bis(dimethyl-amino)methane (Bredereck′s reagent) was purchased from Acros Organics. Hydrogen gas (≥ 99.999%) was purchased from Linde. All the other reagents were purchased from Sigma-Aldrich and used without further purification. Anhydrous MeOH was purchased from Sigma-Aldrich and used as bought. All the other solvents were bought and used as reagent grade.

Reaction details: Unless otherwise stated, all reactions were conducted under nitrogen. Reactions run in room temperature were in the range of 20-23 °C. Heating plates with temperature control and metal heating blocks were used when the reaction temperature was higher than room temperature. For the reactions run at 0 °C, an ice bath was used when the reaction time was shorter than 6 h, and a Julabo FT902 Immersion Cooler was used with EtOH as the cooling media when the reaction time was longer than 6 h. The pressurized hydrogenation reactions were conducted in a Straus flask equipped with a magnetic stir bar. The pressure in the hydrogenation reactions was generated by filling in hydrogen at -196 ºC and warming the sealed flask slowly to room temperature. All the other reaction were conducted in a round bottom flask equipped with a magnetic stir bar.

Chromatography: Analytical thin-layer chromatography (TLC) was carried out on Merck TLC Silica Gel 60 F_{254} and visualized with a UV-lamp (254 nm) or potassium permanganate stain. Silica gel column chromatography was performed with silica gel from Sigma-Aldrich (60 Å, 230-400 mesh) and reagent-grade solvents. Ion-exchange column chromatography was performed with ion-exchange resin (DOWEX® 50WX4-200) and deionized water (ø = 3 cm, h = 6 cm). Preparative reverse phase HPLC for the purification of *rac*-**1** and (+)-(*SSS*)-**1** was performed using an Agilent Infinity 1260 HPLC with Waters XSelect® CSH™ Prep C18 coulumn (5 μm, OBD™, 19x250 mm). Preparative chiral separation of *rac*-**16** and all the analytical chiral HPLC were performed by CHIRAL TECHNOLOGIES EUROPE, France.

NMR spectroscopy: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II at 400.1 MHz and 100.6 MHz, respectively. The spectra were recorded in $CDCl_3$ and referenced to residual $CDCl_3$ (δ 7.26 ^{1}H; 77.16 ^{13}C) or DMSO-d_6 and referenced to residual DMSO-d_6 (2.50 ^{1}H; 39.52 ^{13}C). Chemical shifts (δ) are expressed in parts per million (ppm) and coupling

constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to indicate apparent multiplicities: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; m, multiplet.

Melting points: Melting points were measured using a Stuart SMP3 Melting Point Apparatus.

IR spectroscopy: IR transmittance spectra were recorded on a Bruker ALPHA FT-IR Spectrometer and reported in cm^{-1}. The following abbreviations were used to indicate the peak shape or peak intensity: br, broad; s, strong; m, moderate; w, weak.

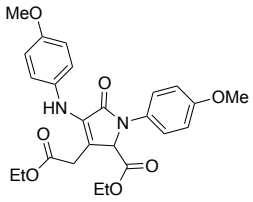
Mass spectroscopy: High resolution mass spectroscopy (HRMS) was carried out using a Waters Xevo-G2 QTof Spectrometer using electron spray (ESI) ionization and was run in positive mode.

Elemental analysis: Elemental analyses were performed by A. Kolbe, Mikroanalytisches Laboratorium, Germany.

Specific rotation: Specific rotations $[\alpha]_D^T$ were measured a using Bellingham + Stanley Single Wavelength Polarimeter ADP450 at 25 °C. D represents the sodium D line (589 nm). Concentrations were reported in g/mL.

Circular dichroism: Circular dichroism spectra were recorded on a Jasco J-815 Circular Dichroism Spectropolarimeter under the following conditions: bandwidth, 1 nm; scan rate, 100 $nm \cdot min^{-1}$; accumulation, 3 times; data interval, 1 nm; cell length, 2 mm; temperature, 20 °C

2. *Experimental procedures and analytical data for rac-**12**, rac-**13**, rac-**14**, rac-**15**, rac-**16**, (-)-**16**, rac-**1** and (+)-(SSS)-**1***



***rac*-Ethyl 3-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate (*rac*-12)**

To a slurry of $MgSO_4$ (50.0 g) and 4-anisidine (7.39 g, 60.0 mmol) in AcOH (400 mL) was added ethyl 2-oxoacetate (5.61 M in toluene, 5.30 mL, 30.0 mmol) and diethyl 2-oxopentanedioate (18.2 g, 16.4 mL, 90.0 mmol). The resulted yellow slurry was stirred for 6 h at room temperature. The reaction mixture was filtered, and the solid residue was washed with EtOAc. The combined filtrate was concentrated under reduced pressure, giving a viscous reddish oil. The crude was subjected to a silica column (ø = 8 cm, h = 10 cm, *n*-heptane/EtOAc, 2 : 1, v/v), resulting in *rac*-**12** as a viscous yellow oil (10.7 g, 76%) which turned to sticky yellow solid over time under vacuum. Further recrystallization with EtOH afforded *rac*-**12** as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.44 (m, 2H), 7.06 – 6.97 (m, 2H), 6.95 – 6.87 (m, 2H), 6.86 – 6.78 (m, 2H), 6.02 (s, 1H), 5.23 (s, 1H), 4.20 – 4.01 (m, 4H), 3.80 (s, 3H), 3.79 (s, 3H), 3.18 (d, J = 17.9 Hz, 1H), 2.99 (dd, J = 17.9, 1.1 Hz, 1H), 1.21 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.97, 168.70, 166.95, 157.28, 156.68, 134.67, 133.31, 130.86, 124.61, 122.83, 114.48, 114.43, 106.27, 64.98, 62.00, 61.13, 55.60, 55.57, 31.60, 14.26, 14.12 ppm.

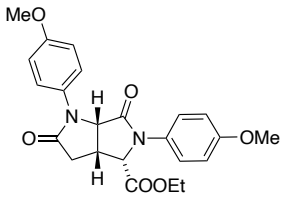
HRMS (ESI+) m/z: $[M+H]^+$ Calcd for $C_{25}H_{29}N_2O_7$ 469.1975; Found 469.1973.

Elemental analysis Calcd (%) for $C_{25}H_{28}N_2O_7$: C 64.09, H 6.02, N 5.98; Found: C 63.84, H 6.01, N 5.95.

IR (neat) ν_{max} 3319 (br), 1734 (m), 1696 (m), 1513 (s), 1246 (m), 1182 (m), 1030 (m) cm^{-1}.

Melting point: 113-114 °C.

R_f = 0.2 (*n*-heptane/EtOAc, 2 : 1, v/v).



***rac*-Ethyl (3a*R**,4*S**,6a*S**)-1,5-bis(4-methoxyphenyl)-2,6-dioxooctahydropyrrolo[3,4-*b*]pyrole-4-carboxylate (*rac*-13)**

To a slurry of *rac*-**12** (2.00 g, 4.26 mmol) in anhydrous MeOH (60.0 mL) was carefully added palladium on activated charcoal (10 wt. %, 454 mg, 0.426 mmol). The mixture was stirred at room temperature under H_2 (~4 atm) for three days. After that time the reaction vessel was carefully opened to air. The reaction mixture was filtered through a pad of celite. The celite was washed with $CHCl_3$ (2 x 30 mL). The combined filtrate was concentrated under reduced pressure, resulting in a viscous yellow oil or a sticky yellow solid in quantitative yield.

To this product (17.6 g, 37.4 mmol) was added AcOH (200 mL), and the resulting mixture was stirred at 60 °C overnight. The next day, the reaction mixture was concentrated under reduced pressure, giving in yellowish solid. Further recrystallization with EtOH afforded *rac*-**13** as a white solid (12.6 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.46 (m, 2H), 7.31 – 7.26 (m, 2H), 6.98 – 6.81 (m, 4H), 4.92 (dd, J = 8.5, 1.3 Hz, 1H), 4.71 (dd, J = 8.3, 2.1 Hz, 1H), 4.28 – 4.06 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.54 (ddd, J = 9.1, 6.7, 2.4 Hz, 1H), 2.78 – 2.60 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.91, 169.05, 168.92, 158.07, 158.00, 130.19, 130.15, 125.85, 124.33, 114.31, 114.29, 64.02, 62.96, 62.31, 55.50, 55.49, 33.13, 31.55, 14.17 ppm.

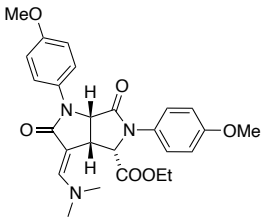
HRMS (ESI+) m/z: $[M+H]^+$ Calcd for $C_{23}H_{25}N_2O_6$ 425.1713; Found 425.1706.

Elemental analysis Calcd (%) for $C_{23}H_{24}N_2O_6$: C 65.08, H 5.70, N 6.60; Found: C 64.74, H 5.76, N 6.55.

IR (neat) ν_{max} 1739 (m), 1694 (s), 1509 (s), 1379 (m), 1243 (s), 1181 (m), 1027 (s) cm^{-1}.

Melting point: 179-180 °C.

R_f = 0.4 (EtOAc).



***rac*-Ethyl (3a*R**,4*S**,6a*S**,*E*)-3-((dimethylamino)methylene)-1,5-bis(4-methoxyphenyl)-2,6-dioxooctahydropyrrolo[3,4-*b*]pyrrole-4-carboxylate (*rac*-14)**

To a slurry of *rac*-**13** (12.6 g, 29.7 mmol) in toluene (50.0 mL) was added *tert*-butoxy bis(dimethylamino)methane (Bredereck's reagent, 24.5 mL, 119 mmol). The mixture was heated to 110 °C and stirred at this temperature overnight. The next day, TLC indicated that the starting material was consumed. The reaction mixture was concentrated under reduced pressure, giving a white yellow solid as crude. Recrystallization of the crude with boiling EtOAc afforded *rac*-**14** (5.14 g) as off-white crystals. The filtrate was concentrated under reduced pressure and subjected to a silica column (ø = 4.5 cm, h = 10 cm, EtOAc : MeOH = 15 : 1), giving *rac*-**14** as a light-yellow solid (2.17 g, in total 7.31 g, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.33 – 7.27 (m, 2H), 7.10 (d, *J* = 1.2 Hz, 1H), 6.90 – 6.85 (m, 2H), 6.83 – 6.76 (m, 2H), 4.74 (d, *J* = 9.5 Hz, 1H), 4.61 (d, *J* = 8.7 Hz, 1H), 4.37 – 4.24 (m, 1H), 4.09 – 3.98 (m, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.01 (s, 6H), 1.14 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.76, 169.53, 169.41, 157.57, 157.14, 145.20, 131.06, 130.52, 125.86, 124.07, 114.11, 113.80, 91.33, 77.16, 69.20, 61.69, 61.06, 55.33, 55.30, 41.80, 35.02, 13.93 ppm.

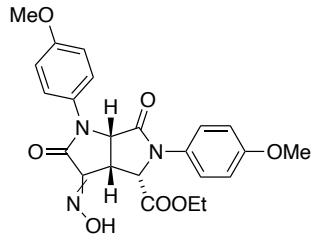
HRMS (ESI+) m/z: $[M+H]^+$ Calcd for $C_{26}H_{30}N_3O_6$ 480.2135; Found 480.2134.

Elemental analysis Calcd (%) for $C_{26}H_{29}N_3O_6$: C 65.12, H 6.10, N 8.76; Found: C 64.89, H 6.07, N 8.63.

IR (neat) ν_{max} 1740 (w), 1682 (m), 1617 (m), 1509 (s), 1357 (m), 1243 (s), 1180 (m), 1029 (m) cm^{-1}.

Melting point: 200-201 °C.

R_f = 0.2 (EtOAc).



rac-Ethyl(3a*R,4*S**,6a*S**)-3-(hydroxyimino)-1,5-bis(4-methoxyphenyl)-2,6-dioxoocta-hydro-pyrrolo[3,4-*b*]pyrrole-4-carboxylate (E/Z isomer)** (***rac*-15**)

To a solution of *rac*-**14** (5.50 g, 11.5 mmol) in diluted AcOH (200 mL, 10% H_2O, v/v) at 0 °C was added dropwise an aqueous solution of $NaNO_2$ (0.5 M, 29.9 mL). The reaction was stirred at 0 °C for three days, during which time the reaction mixture turned from a clear solution to a white slurry. After three days, the reaction mixture was filtered. The solid was washed with ice-cold EtOH (2 x 50 mL) and dried under vacuum, affording *rac*-**15** as a white solid (4.75 g, 90%). Compound *rac*-**15** was obtained as a mixture of *E*/*Z* isomers. The ratio between *E*- and *Z*-isomer varied among batches, and the *E*- isomer was found to be the major isomer. The ^{1}H NMR and ^{13}C NMR peaks that belongs to the *E*-isomer are reported below.

^{1}H NMR (400 MHz, DMSO) δ 12.50 (s, 1H), 7.44 (d, J = 9.0 Hz, 2H), 7.28 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 9.1 Hz, 2H), 6.93 (d, J = 9.1 Hz, 2H), 5.31 (d, J = 9.8 Hz, 1H), 5.05 (d, J = 8.5 Hz, 1H), 4.38 (dd, J = 9.8, 8.5 Hz, 2H), 3.92 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 1.06 (t, J = 7.1 Hz, 1H) ppm. ^{13}C NMR (101 MHz, DMSO) δ 169.11, 167.93, 161.82, 157.64, 150.23, 130.01, 129.49, 126.14, 125.24, 114.16, 113.83, 63.18, 61.33, 59.56, 55.31, 55.28, 31.85, 13.64 ppm.

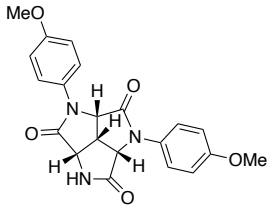
HRMS (ESI+) m/z: $[M+H]^+$ Calcd for $C_{24}H_{25}N_2O_7$ 453.1662; Found 453.1660.

Elemental analysis Calcd (%) for $C_{24}H_{24}N_2O_7$: C 60.92, H 5.11, N 9.27; Found: C 61.02, H 5.15, N 9.19.

IR (neat) ν_{max} 3200 (w, br), 1738 (m), 1692 (s), 1516 (s), 1253 (s), 1190 (m), 1029 (m) cm^{-1}.

Melting point: Decomposes at 216 °C.

R_f: 0.35 (EtOAc).



rac*-(2a*S**,2a^1*S**,4a*S**,6a*S**)-1,3-bis(4-methoxyphenyl)hexahydro-1,3,5-triazacyclopenta-[*cd*]-pentalene-2,4,6(1*H*)-trione** (rac*-16**)

To a slurry of *rac*-**15** (500 mg, 1.10 mmol) in AcOH (30.0 mL) was carefully added palladium on activated charcoal (10 wt. %, 117 mg, 0.110 mmol). The mixture was stirred at 70 °C under H_2 (4 atm) for five days. After that time the reaction was cooled to room temperature and the vessel was carefully opened to air. The reaction mixture was filtered through a pad of celite. The celite was washed with $CHCl_3$ (2 x 20 mL). The combined filtrate was concentrated under reduced pressure, resulting in a light-yellow solid, which was precipitated in EtOH. The precipitate was filtered and dried, affording *rac*-**16** as a white solid (345 mg, 79%).

^{1}H NMR (400 MHz, DMSO) δ 8.97 (s, 1H), 7.52 – 7.39 (m, 4H), 7.02 – 6.87 (m, 4H), 4.93 (d, *J* = 9.9 Hz, 1H), 4.79 (d, *J* = 9.7 Hz, 1H), 4.31 (dd, *J* = 9.6, 1.4 Hz, 1H), 3.94 (q, *J* = 9.7 Hz, 1H), 3.76 (d, *J* = 9.1 Hz, 6H) ppm.

^{13}C NMR (101 MHz, DMSO) δ 172.17, 171.09, 169.12, 157.42, 157.13, 130.39, 130.28, 126.08, 125.47, 113.78, 113.61, 62.02, 60.56, 56.25, 55.26, 55.21, 31.45 ppm.

HRMS (ESI+) m/z: $[M+H]^+$ Calcd for $C_{21}H_{20}N_3O_5$ 394.1403; Found 453.1396.

Elemental analysis Calcd (%) for $C_{21}H_{19}N_3O_5$: C 64.12, H 4.87, N 10.68; Found: C 63.72, H 4.97, N 10.63.

IR (neat) ν_{max} 3246 (br), 1696 (s), 1512 (s), 1249 (m), 1180 (w), 1031 (w) cm^{-1}.

Melting point: Decomposes at 233 °C.

R$_f$ = 0.3 (MeOH/EtOAc, 1 : 9, v/v).

Resolution of *rac*-16 by chiral preparative HPLC

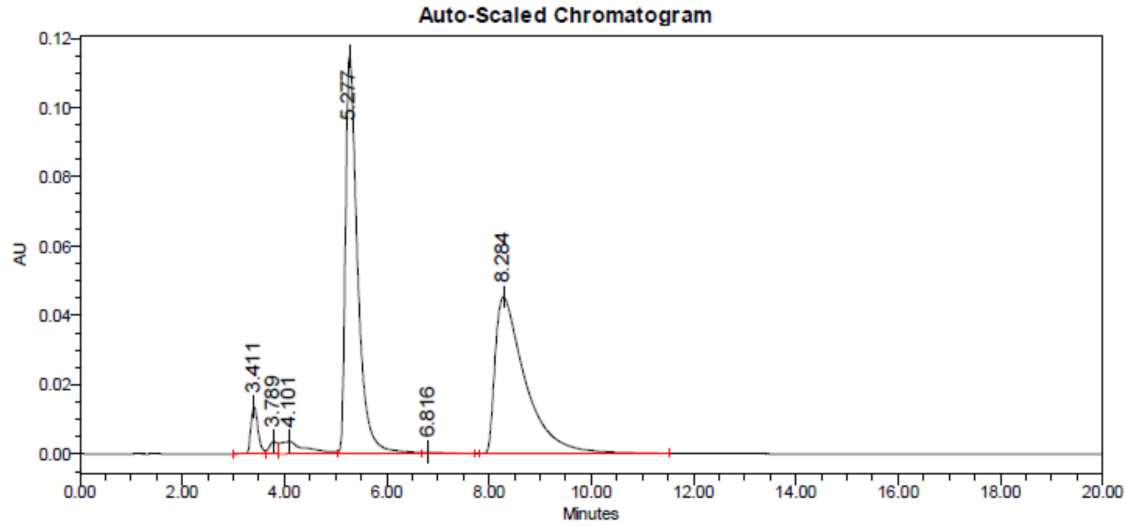
The racemic compound *rac*-**16** (998.6 mg) was separated by preparative HPLC, yielding (–)-**16** as a white powder (453.2 mg, 90%, *ee* > 99%, $[\alpha]_D^{25}$: -69.8 (*c* = 1.00 in MeCN)) and (+)-**16** as a white powder (448.7 mg, 89%, *ee* > 99%).

Preparative chiral HPLC method: CHIRALPAK®IA 5 μm – 250 x 30 mm, MeCN, flow rate

= 42.4 mL/min, λ = 290 nm, T = 25 °C, t_R = 5.3 min (major), 8.3 min (minor)

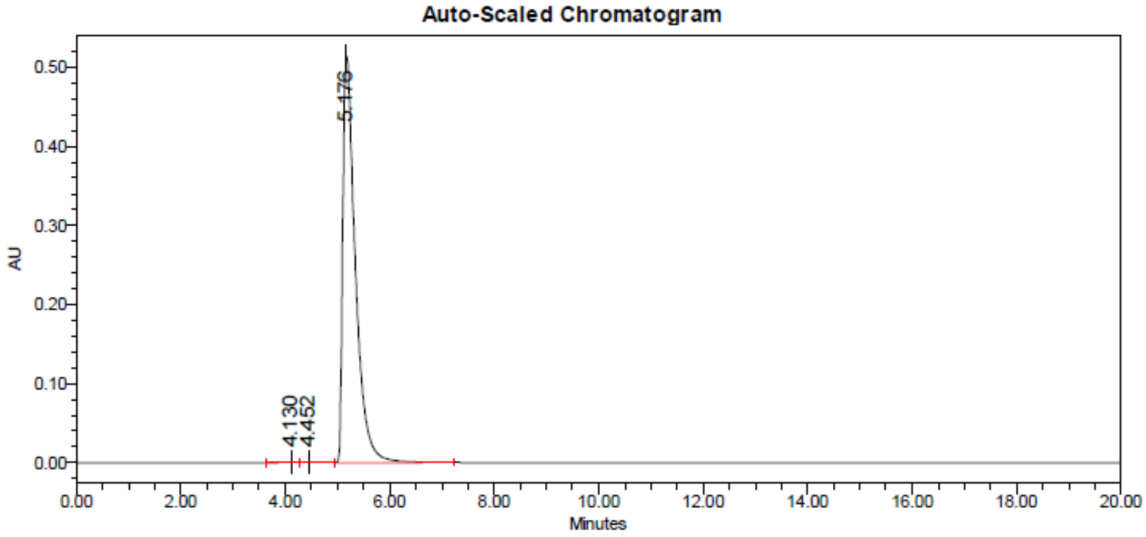
Analytical chiral HPLC method: CHIRALPAK®IA 5 μm – 250 x 4.6 mm, MeCN, flow rate = 1.0 mL/min, λ = 290 nm, T = 25 °C, t_R = 5.3 min (major), 8.3 min (minor).

Table S1. HPLC chromatogram of *rac*-**16**.



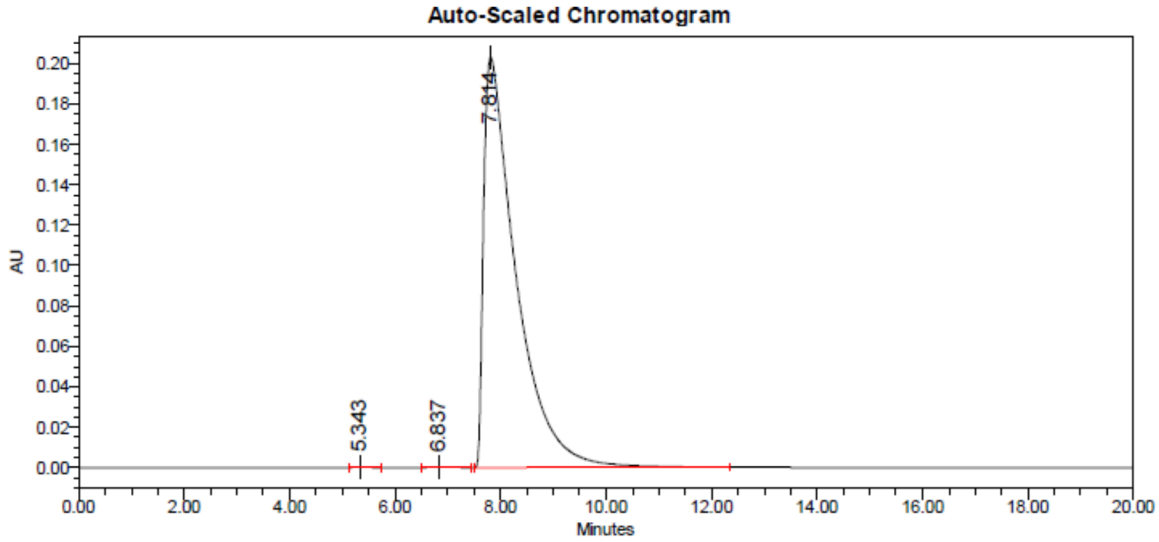
Peak	Retention time (min)	Area (%)
1	5.277	50.51
2	8.284	49.49

Table S2. HPLC chromatogram of (–)-**16**.

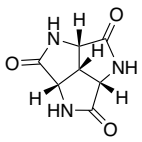


Peak	Retention time (min)	Area (%)
1	5.176	100
2	-	LoD

Table S3. HPLC chromatogram of (+)-**16**.



Peak	Retention time (min)	Area (%)
1	-	LoD
2	7.814	100



***rac*-(2a*S**,4a*S**,6a*S**)-hexahydro-1,3,5-triazacyclopenta[*cd*]pentalene-2,4,6(1*H*)-trione (*rac*-1)**

To a slurry of **16** (393 mg, 1.00 mmol) in MeCN (5.00 mL) at 0 °C was added dropwise an aqueous solution of cerium ammonium nitrate (CAN) (3.62 g CAN dissolved in 5.00 mL water, 6.60 mmol). The mixture was stirred at 0 °C for 1 h. The crude was concentrated to one third volume under reduced pressure and subjected to ionic exchange chromatography, yielding a yellowish solid which was further purified by preparative reverse phase HPLC. The product was obtained as a white crystalline solid (113 mg, 62%).

Preparative reverse phase HPLC method: Programmed elution from H_2O (with 0.1% HCOOH)/MeCN 95:5 to pure MeCN, 20.0 mL/min, λ = 224 nm, T = 25 °C. The product was eluted from 2.6 min to 3.5 min.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 3H), 3.98 (dd, J = 9.4, 1.3 Hz, 3H), 3.76 – 3.68 (m, 1H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ 174.02, 55.85, 35.58 ppm.

HRMS (ESI+) m/z: $[M+H]^+$ Calcd for $C_7H_8N_3O_3$ 182.0566; Found 182.0560.

Elemental analysis Calcd (%) for $C_7H_7N_3O_3$: C 46.41, H 3.90, N 23.20; Found: C 46.37, H 3.89, N 23.19.

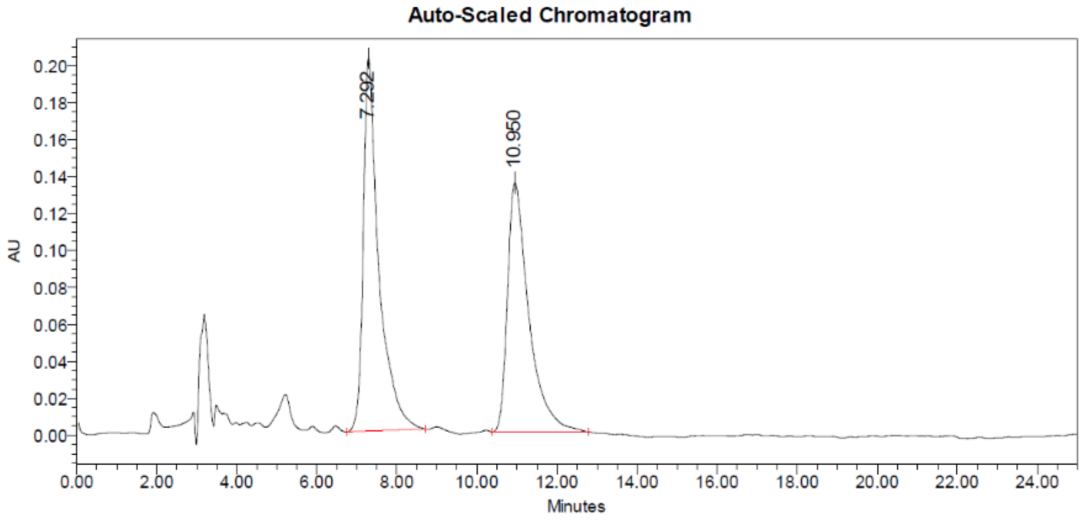
IR (neat) ν_{max} 3212 (br), 1662 (m), 1415 (m), 1298 (m), 1260 (m), 1091 (m), 1007 (w) cm^{-1}.

Melting point: >250 °C.

R_f: 0.3 (MeOH/EtOAc, 1 : 1, v/v). Stains yellow with $KMnO_4$ stain after heating to > 200 °C.

Analytical chiral HPLC method: CHIRALPAK®IA 5 μm – 250 x 4.6 mm, MeOH/EtOH (1 : 1, v/v), flow rate = 1.0 mL/min, λ = 200 nm, T = 25 °C, t_R = 7.3 min (major), 11.0 min (minor).

Table S4. HPLC chromatogram of *rac*-**1**.



Peak	Retention time (min)	Area (%)
1	7.292	52.29
2	10.950	47.71

(+)-(2a*S*,4a*S*,6a*S*)-hexahydro-1,3,5-triazacyclopenta[*cd*]pentalene-2,4,6(1*H*)-trione ((+)-(*SSS*)-1)

To a slurry of (–)-**16** (393 mg, 1.00 mmol) in MeCN (5.00 mL) at 0 °C was added dropwise an aqueos solution of cerium ammonium nitrate (CAN) (3.62 g CAN dissolved in 5.00 mL water, 6.60 mmol). The mixture was stirred at 0 °C for 1 h. The crude was concentrated to one third volume under reduced vacuum and subjected to an ionic exchange column, yielding a yellowish solid which was further purified by preparative reverse phase HPLC. The product was obtained as a white crystalline solid (98.0 mg, 54%).

Preparative reverse phase HPLC method: Programmed elution from H_2O (with 0.1% HCOOH)/MeCN (95 : 5, v/v) to pure MeCN, 20.0 mL/min, λ = 224 nm, T = 25 ºC. The product was eluted from 2.6 min to 3.5 min.

^{1}H NMR (400 MHz, DMSO) δ 8.73 (s, 3H), 3.98 (dd, J = 9.4, 1.3 Hz, 3H), 3.78 – 3.67 (m, 1H) ppm.

^{13}C NMR (101 MHz, DMSO) δ 174.00, 55.83, 35.56 ppm.

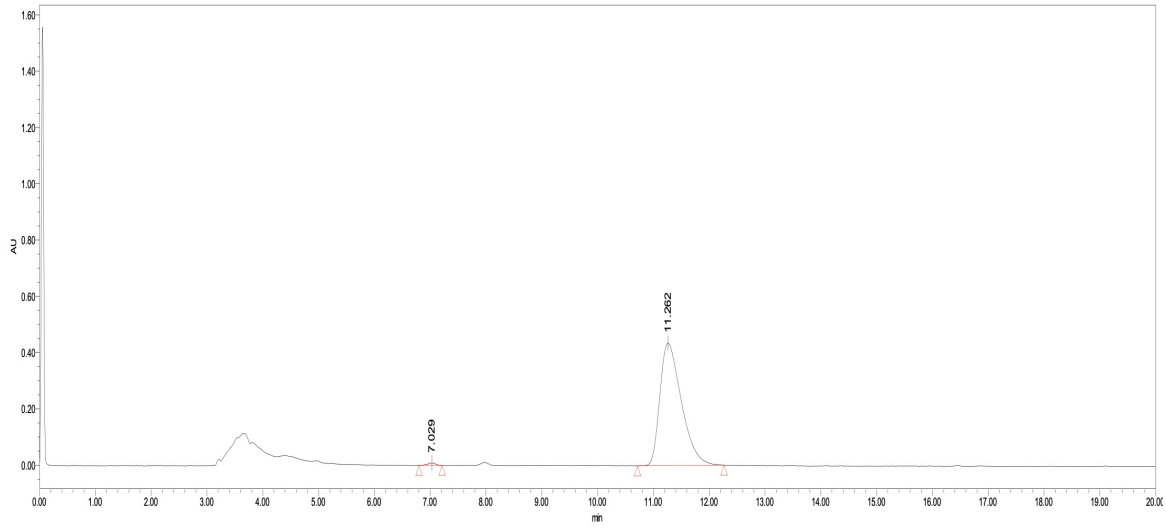
HRMS (ESI+) m/z: $[M+Na]^+$ Calcd for $C_7H_8N_3O_3$ 204.0385; Found 204.0382.

R$_f$: 0.3 (MeOH/EtOAc, 1 : 1, v/v). Stains yellow with $KMnO_4$ stain under heat over 200 °C.

Optical rotation: $[\alpha]_D^{25}$: 53.4 (c = 1.00 in H_2O)

Analytical chiral HPLC method: CHIRALPAK®IA 5 μm – 250 x 4.6 mm, MeOH/EtOH (1 : 1, v/v), flow rate = 1.0 mL/min, λ = 210 nm, T = 25 ºC, t_R = 11.3 min.

Table S5. HPLC chromatogram of (+)-**1**.



Peak	Retention time (min)	Area (%)
1	-	LoD
2	11.282	100

*3. Assignment of the absolute configuration of (+)-**1***

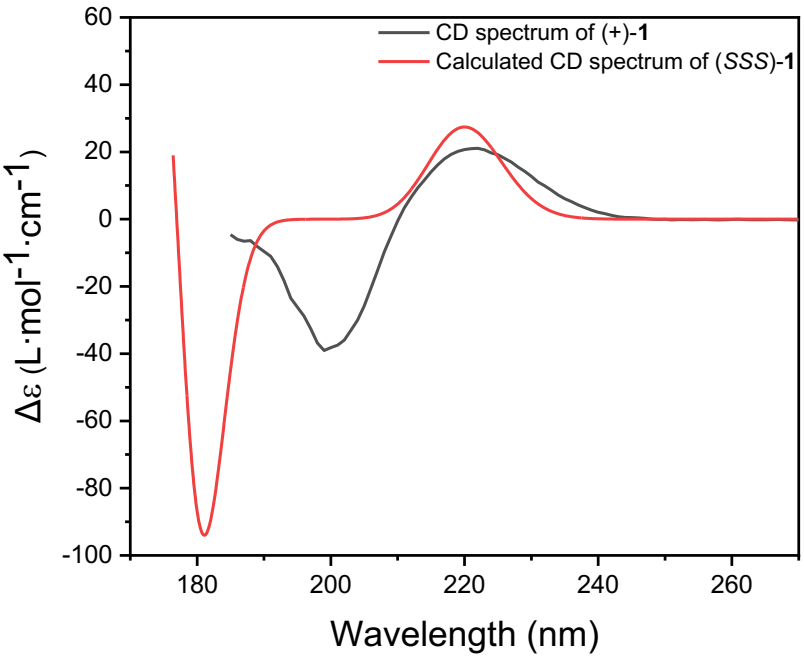


Figure S1. Experimental (gray) and calculated (red) molar circular extinction of (+)-**1**.

Experimental molar circular extinction:

The calculation of the molar circular extinction was done by the following equation:

$$\Delta\varepsilon = \frac{mdeg * M}{c * l * 32.98 * 1000}$$

where *mdeg* is the reported millidegrees from the CD experiment, *M* is the molecular weight of the compound (181.15 g/mol), *c* is the concentration of the solution (0.06 g/L), *l* is the path length of the light (0.2 cm), and $\Delta\varepsilon$ is the difference of extinction coefficients for left and right circularly polarized light, respectively.

Technical Details of the Calculations:

The quantum chemical calculations were carried out with the TURBOMOLE suite of programs. [2] The C_3 symmetric structure of the compound was fully optimized at the dispersion-corrected DFT level using the recent r2SCAN-3c composite density functional [3] employing the COSMO continuum solvation model for water. [4] The COSMO model was also used in all response calculations. Electronic circular dichroism spectra (ECD) as well as optical rotation (OR) at the sodium D-line wavelength $[\alpha]_D$ were computed at the linear response DFT (TDDFT) level [5]

in combination with large augmented AO basis sets (def2-TZVPD [6]) and the wB97X-D3 range-separated hybrid density functional. [7] In the CD calculations, the 20 lowest electronic transitions have been considered that are broadened with Gaussian shape functions of 0.3 eV width at 1/e height for the simulated spectra. The gauge-invariant velocity form was used for the computation of the transition moments while the OR calculations employed the dipole-length form for technical reasons. Test calculations with the velocity form at the PBE/def2-TZVPD level yielded very similar results (difference < 1 % for the OR), indicating that the AO basis set is rather complete.

The results of the CD calculations show, in agreement with the experimental spectra, a medium intensity band of positive CD sign centered around 220 nm resulting from amide type $n \rightarrow \pi^*$ transitions. A negative Cotton effect observed experimentally at about 200 nm is computed with roughly the right negative intensity at about 180 nm and can be assigned to $\pi \rightarrow \pi^*$ transitions. In addition, the computed OR of 70.8 deg/(dm*g/mL) compares well with the experimental value of 53.4 deg/(dm*g/mL) measured in water allowing a definite assignment of the absolute configuration as (+)-*SSS*.

Table S6. Cartesian coordinates of the (+)-*SSS* configuration in Angstrom at the r2SCAN-3c (COSMO, H_2O) level.

Atom	x	y	z
C	0.0377134	-1.4254875	-0.4531351
C	0.0095321	-0.0049442	-1.0518243
N	-1.1387751	-1.4928718	0.4109456
C	1.3357097	-1.4810538	0.3631455
C	-1.2546867	0.6679100	-0.4866497
C	1.1983894	0.7442160	-0.4176235
C	-1.8912445	-0.3849972	0.4254121
N	1.8859247	-0.2610013	0.3865578
H	0.0326411	-2.2307102	-1.1964670
H	0.0391509	-0.0043321	-2.1401477

H	-1.3565134	-2.3125267	0.9770705
O	1.7893848	-2.5082732	0.8926816
H	-1.9734332	1.0058588	-1.2398641
N	-0.7646803	1.7759176	0.3276585
C	0.5637603	1.8504991	0.4372176
H	1.8817838	1.1955506	-1.1455239
O	-2.9246454	-0.1961933	1.0873578
H	2.7188827	-0.0478418	0.9299120
O	1.2006101	2.6767059	1.1109206
H	-1.3895043	2.4335750	0.7899644

*4. Single crystal X-ray diffraction (scXRD) analysis of rac-**13**, rac-**1**-d_3, and (+)-(SSS)-**1***

Single crystals covered in paratone oil were cut to size and mounted on a MiTeGen micro-mount loop. Data collection was performed on an Agilent Xcalibur Sapphire3 or an Agilent Enhance diffractometer equipped with a MoKα high-brilliance IμS radiation source (λ = 0.71073 Å). Absorption was corrected for using multi-scan empirical absorption correction with spherical harmonics as implemented in the SCALE3 ABSPACK scaling algorithm. [8] The structures were solved in WinGX [9] using SUPERFLIP [10] or SHELXL 2016/4 [11] and refined using SHELXL 2016/4. Non-hydrogen atoms were refined anisotropically. A disordered ethyl group in *rac*-**13** was modeled with a refined occupancy over two positions using the PART instruction. Hydrogen bond tables are generated with the HTAB command. Hydrogen bonds from C–H are not included in the tables.

Table S7 Crystal data for *rac*-**13**.[a] *Crystallization:* A solution of *rac*-**13** (17 mg) in EtOAc (5 mL) was slowly evaporated in air. After two days, single crystals suitable for X-ray analysis were obtained.

Chemical formula	$C_{23}H_{24}N_2O_6$	
Formula weight	424.44	
Collection temperature /K	293(2)	
Crystal size /mm^3	0.3 x 0.1 x 0.1	
Crystal habit	colorless, rod	
Wavelength /Å	0.71073	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions:	a = 13.6019(6) Å	α = 90 °
	b = 16.1146(7) Å	β = 91.538(4) °
	c = 9.4624(4) Å	γ = 90 °
Unit cell volume /Å^3	2073.31(16)	
Z, Calculated density /Mg/m^3	4, 1.360	
Radiation type	MoKα	
Absorption coefficient, m/mm^{-1}	0.099	
No. reflections collected / unique	16114 / 4942	
R_{int}	0.0450	
Completeness to theta = 25.000 /%	99.8	
Data / restraints / parameters	4942/ 0 / 303	
Goodness of fit on F^2	1.051	
Final R indices $(I > 2\sigma(I))$	R_1 = 0.0526, wR_2 = 0.1029	
R indices *(all data)*	R_1 = 0.0912, wR_2 = 0.1233	
Absolute structure parameter	–	
Largest diff. peak and hole /e-/Å^3	0.218 and -0.226	
CCDC	2128471	

[a] The ethyl group was modeled as disordered over two positions with a refined population of 55:45.

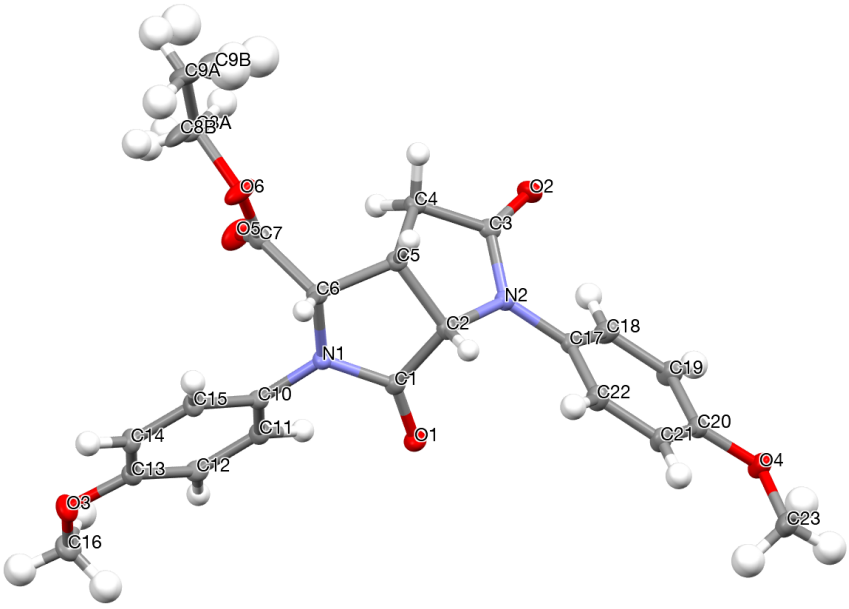


Figure S2. Asymmetric unit of *rac*-**13**. Gray = carbon atom; blue = nitrogen atom; red = oxygen atom; white = hydrogen atom. Thermal ellipsoids are shown at 30% probability.

Table S8. Crystal data for *rac*-**1**-d_3.[a] *Crystallization:* In an NMR tube, a solution of *rac*-**1** (21 mg) in warm D_2O (70 °C, 0.6 mL) was cooled slowly to room temperature with a speed of 3 °C per 30 min. After 5 h, single crystals suitable for X-ray analysis were obtained.

Chemical formula	$C_7H_4D_3N_3O_3$	
Formula weight	184.17	
Collection temperature /K	293(2)	
Crystal size /mm^3	0.3 x 0.2 x 0.1	
Crystal habit	colorless, rod	
Wavelength /Å	0.71073	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions:	a = 7.2905(7) Å	α = 90 °
	b = 11.3194(9) Å	β = 111.738(12) °
	c = 9.0781(10) Å	γ = 90 °
Unit cell volume /Å^3	695.89(13)	
Z, Calculated density /Mg/m^3	4, 1.758	
Radiation type	MoKα	
Absorption coefficient, m/mm^{-1}	0.139	
No. reflections collected / unique	4010 / 1622	
R_{int}	0.0249	
Completeness to theta = 25.000 /%	99.8	
Data / restraints / parameters	1622/ 0 / 127	
Goodness of fit on F^2	1.054	
Final R indices *(I >2σ(I))*	R_1 = 0.0518, wR_2 = 0.1077	
R indices *(all data)*	R_1 = 0.0713, wR_2 = 0.1184	
Absolute structure parameter	–	
Largest diff. peak and hole /e-/Å^3	0.260 and -0.246	
CCDC	2128470	

[a] Because of chemical exchange with D_2O during crystallization, protic groups were modeled with deuterium atoms at the exchanging positions.

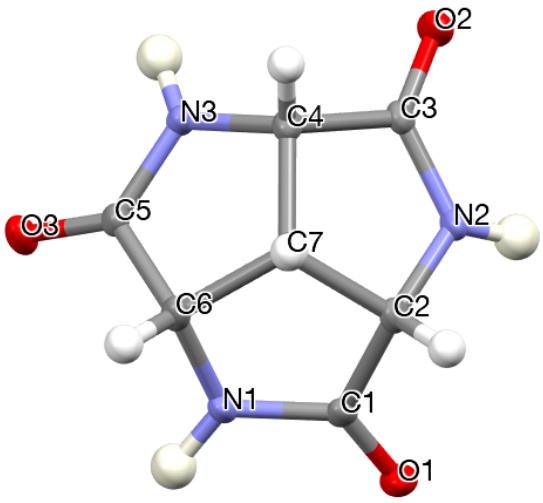


Figure S3. Asymmetric unit of *rac*-**1**-d_3. Gray = carbon atom; blue = nitrogen atom; red = oxygen atom; white = hydrogen/deuterium atom. Thermal ellipsoids are shown at 30% probability.

Table S9. Hydrogen bonds for *rac*-**1** (Å and deg.)[a]

D–H…A	**d(D–H)**	**d(H…A)**	**d(D…A)**	**<(DHA)**
N(3)-D(1)...O(1)#1	0.85(2)	2.58(2)	3.036(2)	114.7(17)
N(3)-D(1)...O(3)#2	0.85(2)	2.21(2)	2.970(2)	149(2)
N(1)-D(2)...O(3)#3	0.91(2)	2.18(2)	2.908(2)	136.3(18)
N(2)-D(3)...O(2)#4	0.82(2)	2.18(2)	2.981(2)	166(2)

(a) Symmetry transformations used to generate equivalent atoms:

#1 [x-1, -y+3/2, z-1/2] **#2** [-x, -y+2, -z+2] **#3** [-x+1, -y+2, -z+2] **#4** [-x, -y+1, -z+2]

Table S10. Crystal data for (+)-(*SSS*)-**1**.[a] *Crystallization:* In an NMR tube, a solution of (+)-(*SSS*)-**1** (10 mg) in water (0.3 mL) was carefully covered by a layer of MeCN (0.5 mL). After 16 h, crystals comprising of intergrowing phases were obtained. Suitable crystals that appeared homogenous in plane polarized light were cut to size with a scalpel and mounted. Data was collected for several crystals, each exhibiting severe twinning. The raised R values reflect overlapping peaks and untreated residual twinning.

Chemical formula	$2(C_7H_7N_3O_3)$, C_2H_3N	
Formula weight	403.36	
Collection temperature /K	293(2)	
Crystal size /mm^3	0.2 x 0.2 x 0.2	
Crystal habit	colorless, irregular	
Wavelength /Å	0.71073	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions:	a = 10.2416(18) Å	α = 90 °
	b = 9.0837(12) Å	β = 117.25(2) °
	c = 10.5564(16) Å	γ = 90 °
Unit cell volume /Å^3	873.1(3)	
Z, Calculated density /Mg/m^3	2, 1.534	
Radiation type	MoKα	
Absorption coefficient, m/mm^{-1}	0.121	
No. reflections collected / unique	10598 / 10598	
R_{int}	*N/a*	
Completeness to theta = 25.000 /%	99.6	
Data / restraints / parameters	10598/ 1 / 266	
Goodness of fit on F^2	1.048	
Final R indices *($I > 2\sigma(I)$)*	R_1 = 0.0784, wR_2 = 0.2705	
R indices *(all data)*	R_1 = 0.1246, wR_2 = 0.2876	
Absolute structure parameter	-0.5(10)	
Largest diff. peak and hole /e-/Å^3	1.482 and -1.198	
CCDC	2128469	

[a] The collected data was indexed as a four-fold twin and the structure modeled with a refined population of 41 : 28 : 28 : 3. The absolute configuration was assigned as described in the supporting information (page S15-17).

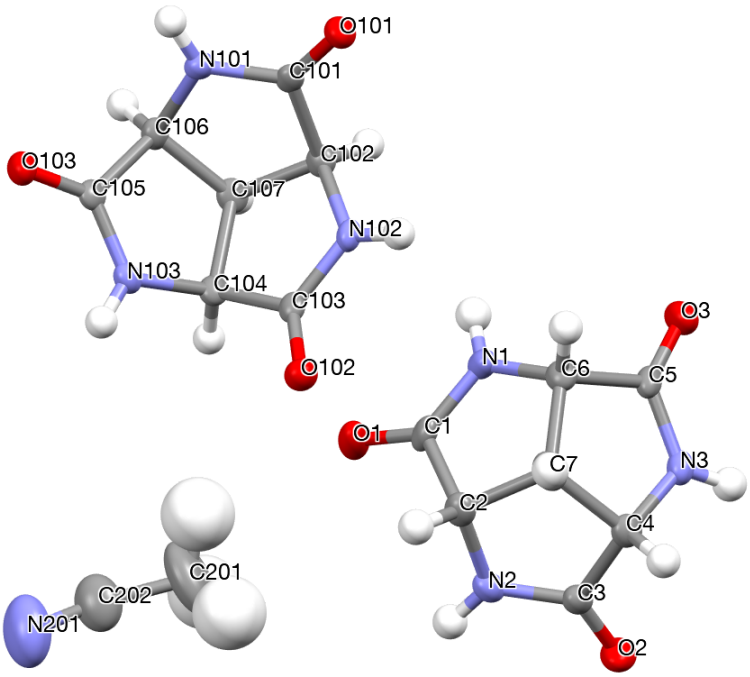


Figure S4. Asymmetric unit of (+)-(*SSS*)-**1**. Gray = carbon atom; blue = nitrogen atom; red = oxygen atom; white = hydrogen atom. Thermal ellipsoids are shown at 30% probability.

Table S11. Hydrogen bonds for (+)-(*SSS*)-**1** (Å and deg.)[a]

D–H…A	d(D–H)	d(H…A)	d(D…A)	<(DHA)
N(1)-H(1A)...O(103) #1	0.86	2.06	2.889(14)	162.0
N(2)-H(2A)...O(102) #2	0.86	2.12	2.966(13)	168.4
N(3)-H(3A)...O(101) #3	0.86	2.06	2.918(14)	175.6
N(101)-H(11A)...O(1) #4	0.86	1.99	2.815(15)	160.7
N(102)-H(12A)...O(3) #5	0.86	1.99	2.828(14)	165.9
N(103)-H(13A)...O(2) #6	0.86	1.92	2.778(13)	171.6

(a) Symmetry transformations used to generate equivalent atoms:

#1 [-x, y+1/2, -z+1] **#2** [-x+1, y+1/2, -z+1] **#3** [-x+1 ,y+1/2, -z+2] **#4** [-x, y-1/2, -z+1]

#5 [-x+1 ,y-1/2, -z+2] **#6** [-x+1, y-1/2, -z+1]

*Modelled self-assembly structures of **1***

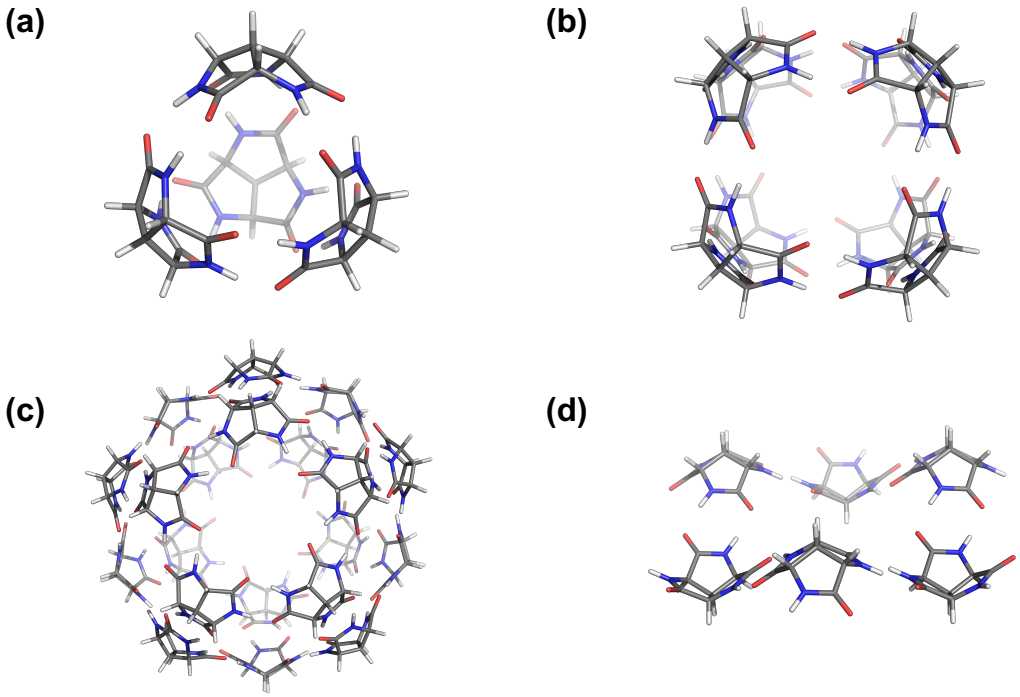


Figure S5. Illustration of possible self-assemblies from trilactam **1**. (a) A tetrahedron assembly (*SSS*)-$\mathbf{1}_4$; (b) A cubic assembly (*SSS*)-$\mathbf{1}_8$; (c) A dodecahedron assembly (*SSS*)-$\mathbf{1}_{20}$; (d) A unit of an infinite non-planar hexagonal tiling that follows the graph set $R_6^6(30)$ consisting of *rac*-**1**;

*5. Preliminary self-assembly studies of rac-**1** and (+)-(SSS)-**1** in solution*

General procedure for self-assemblies of *rac*-1 and (+)-(*SSS*)-1 with argon, methane, nitrogen and xenon

To a solution of the trilactam (0.3 mg) in DMF-d_7 (0.6 mL) in an NMR tube was bubbled the gas through a syringe using a balloon for 30 min. The ^{1}H NMR spectrum of the sample was recorded before and after the bubbling.

General procedure for self-assemblies of *rac*-1 and (+)-(*SSS*)-1 with $CHCl_3$ and MeOH

To a solution of the trilactam (0.3 mg) in DMF-d_7 (0.6 mL) in an NMR tube was added the guest (10 μL). The result mixture was sonicated for 2 min and kept for 30 min. The ^{1}H NMR spectrum of the sample was recorded before the addition and 30 min after the sonication.

6. *Copies of ^{1}H and ^{13}C NMR spectra for rac-**12**, rac-**13**, rac-**14**, rac-**15**, rac-**16**, rac-**1** and (+)-(SSS)-**1**.*

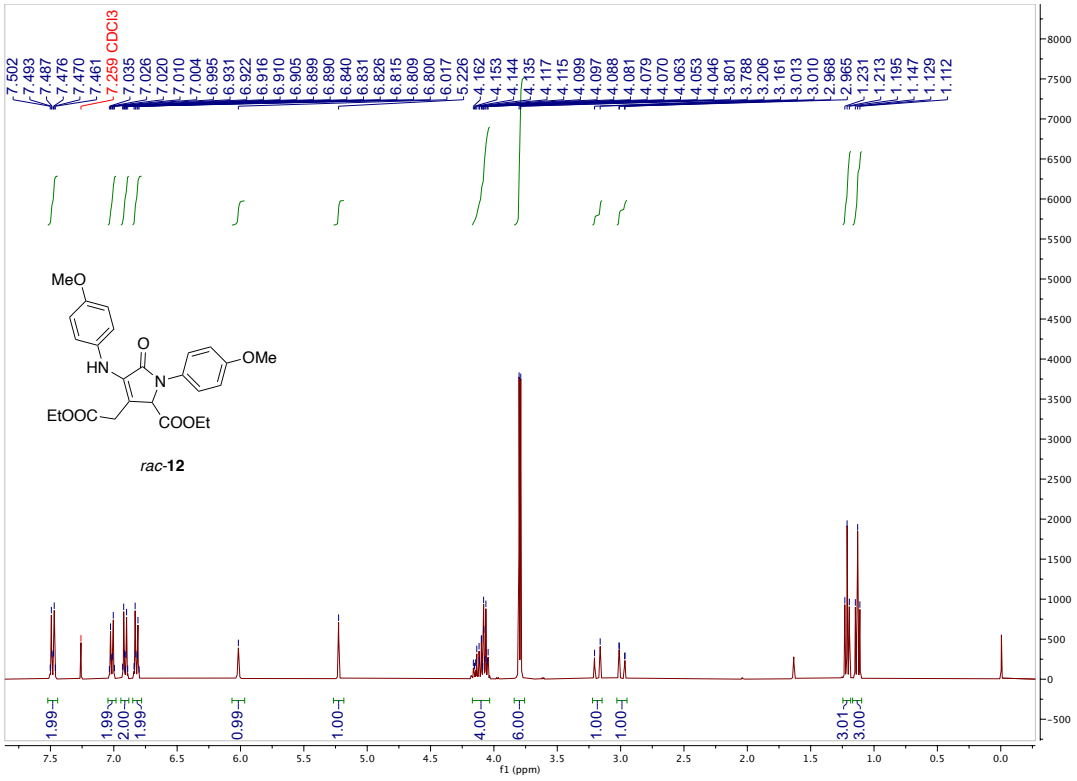


Figure S6. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of *rac*-**12**.

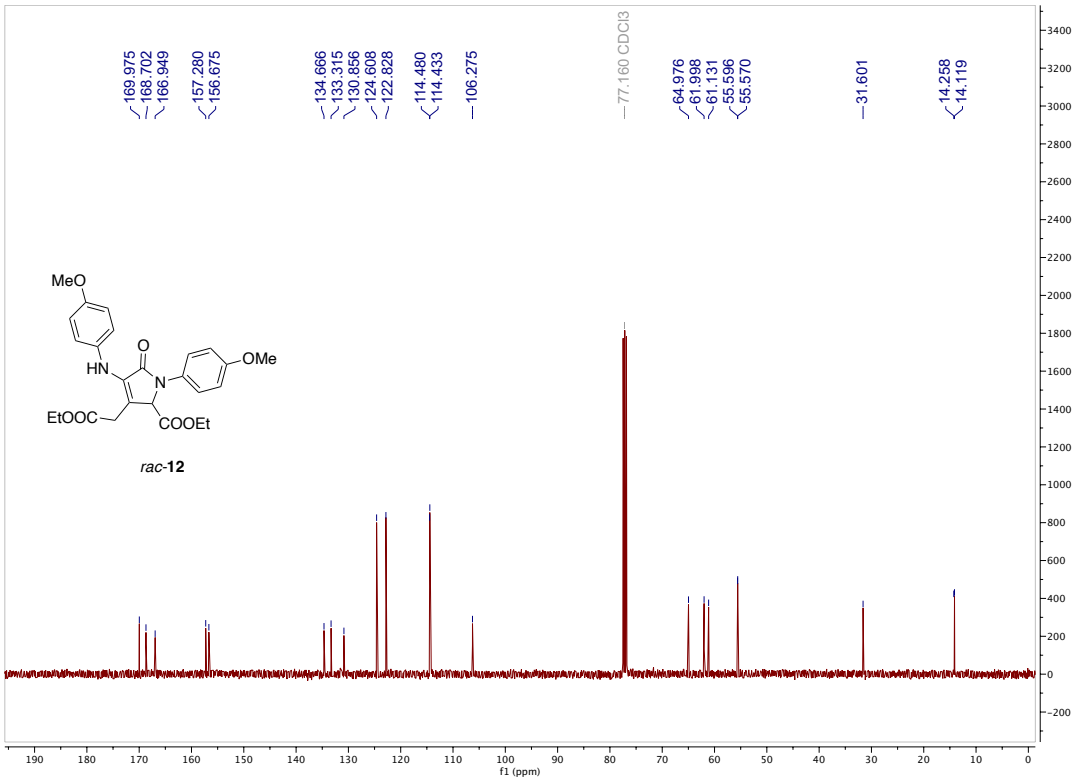


Figure S7. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of *rac*-**12**.

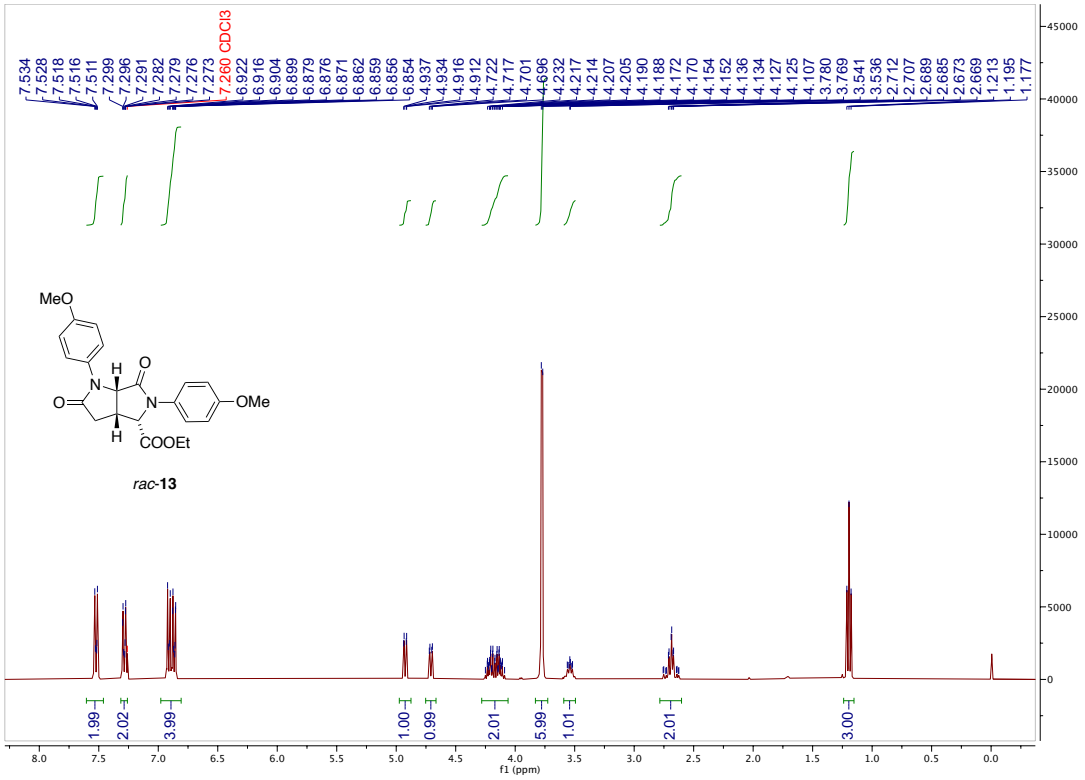


Figure S8. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of *rac*-**13**.

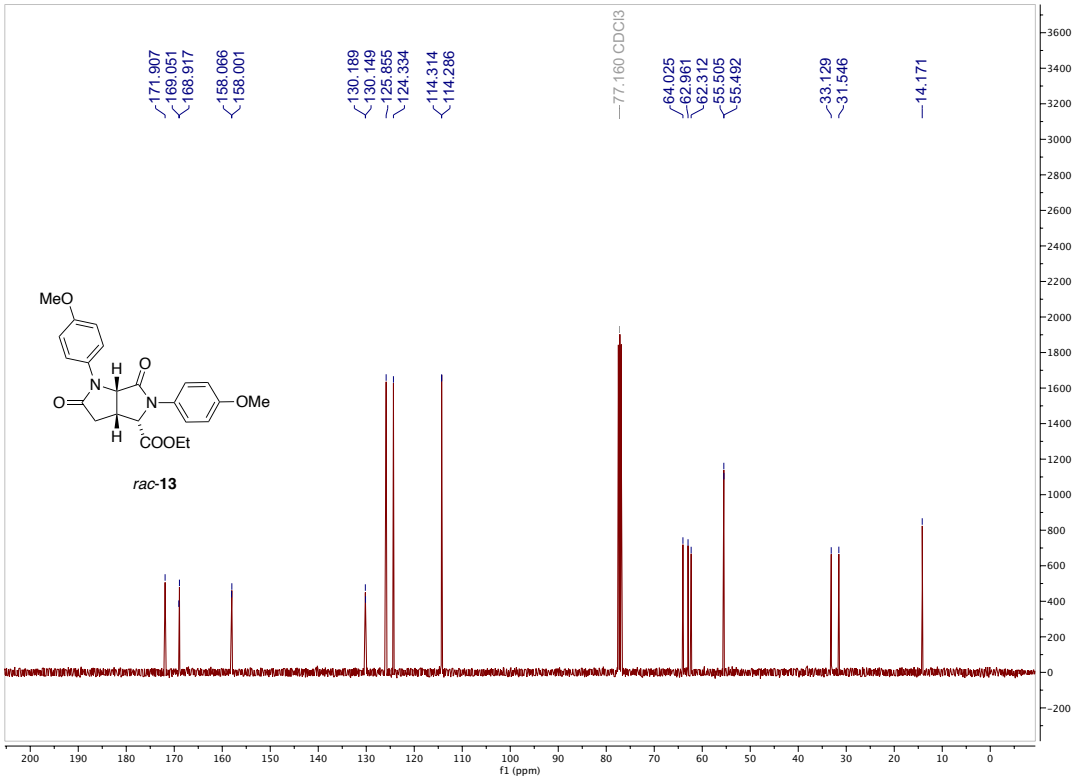


Figure S9. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of *rac*-**12**.

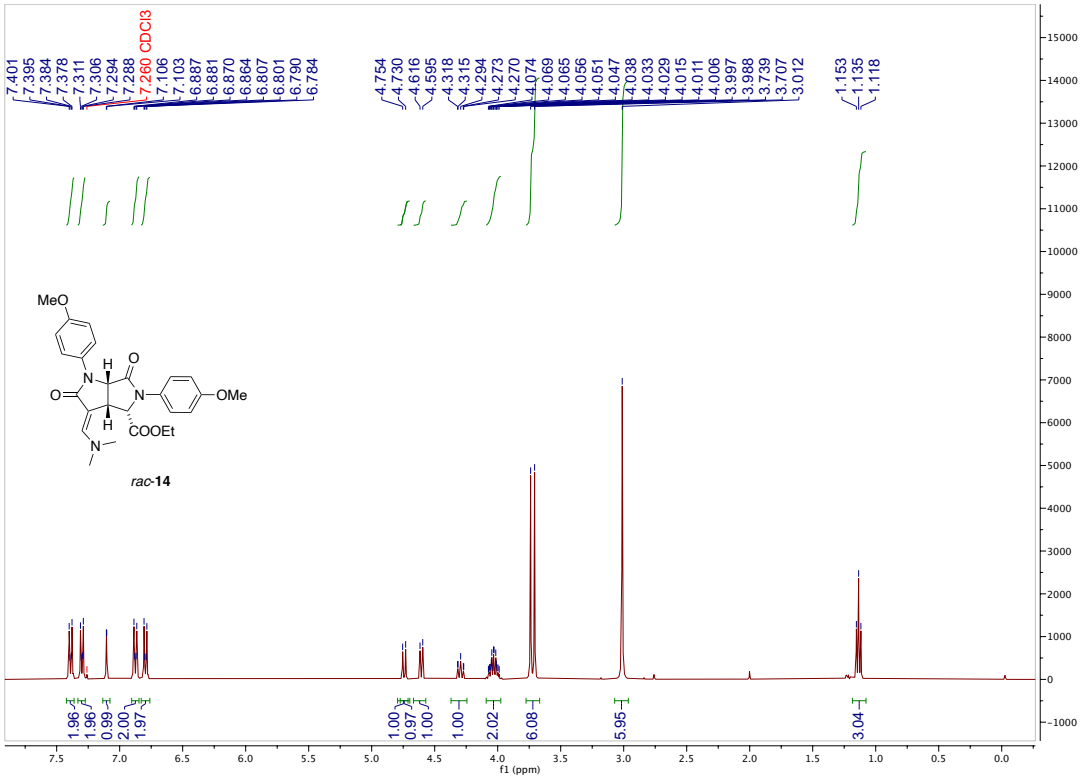


Figure S10. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of *rac*-**14**.

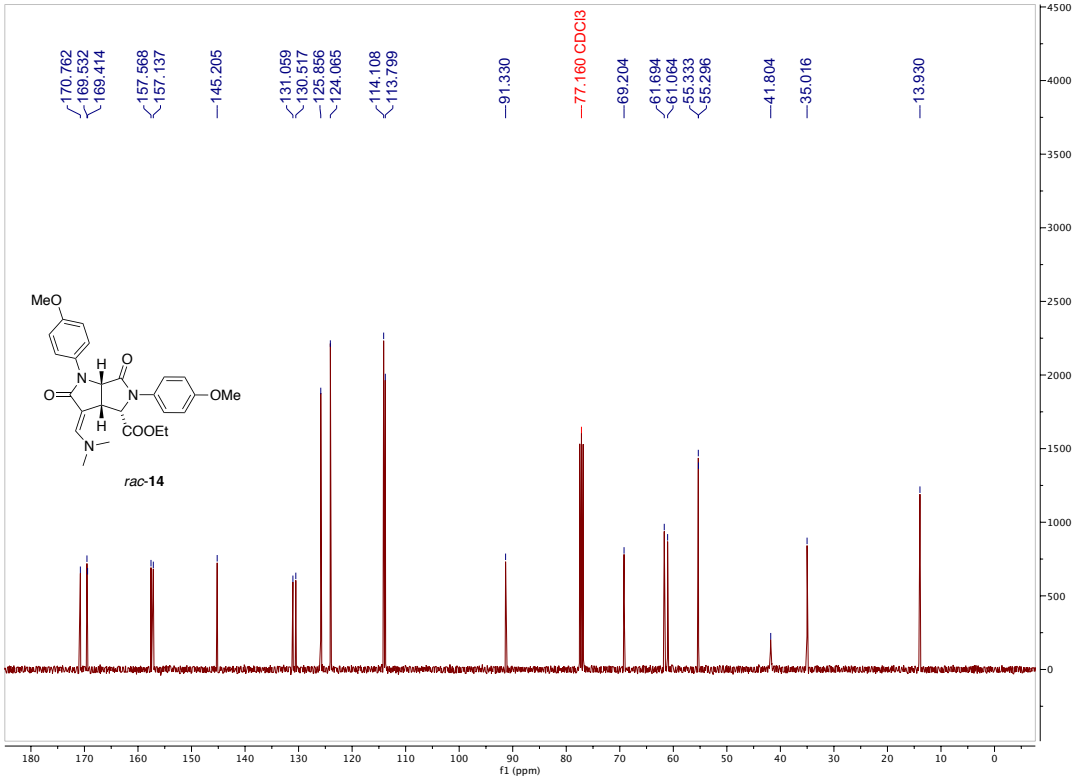


Figure S11. ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of *rac*-**14**.

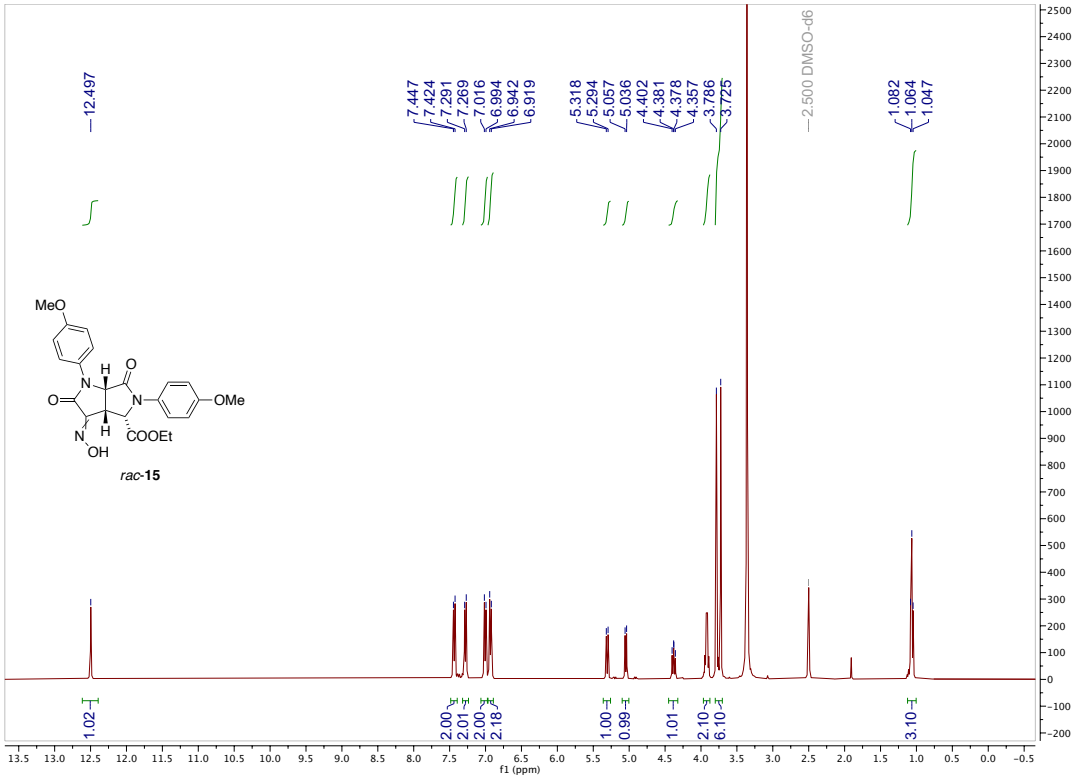


Figure S12. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of *rac*-**15**.

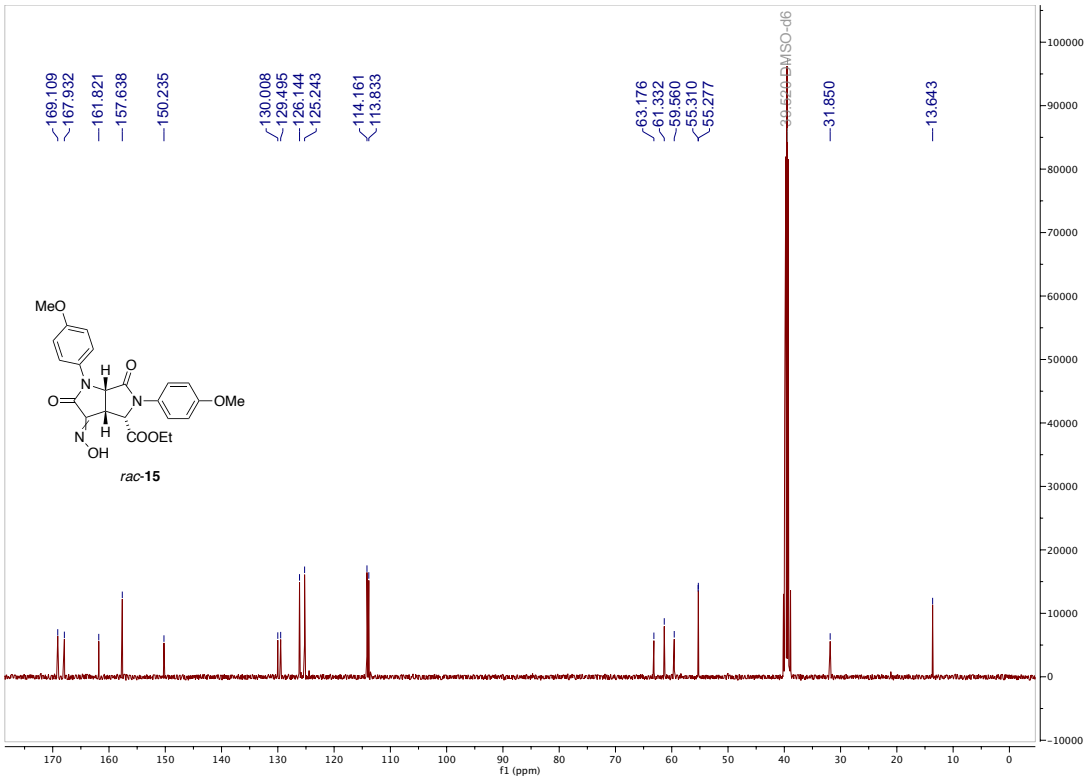


Figure S13. ^{13}C NMR spectrum (101 MHz, DMSO-d_6) of *rac*-**15**.

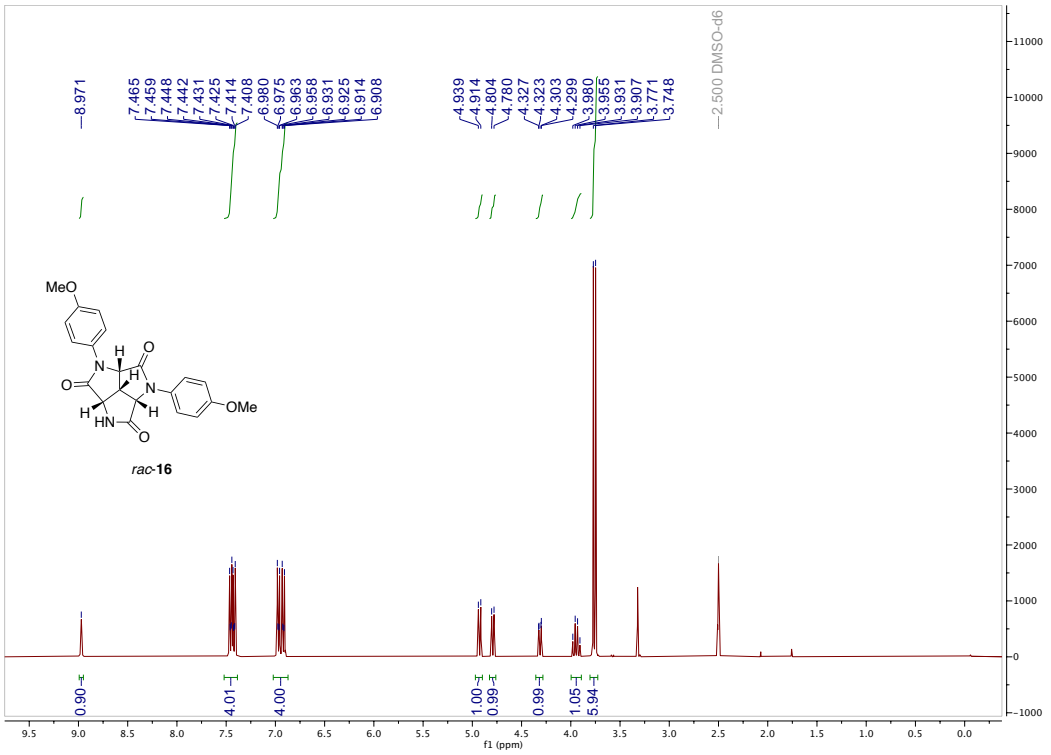


Figure S14. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of *rac*-**16**.

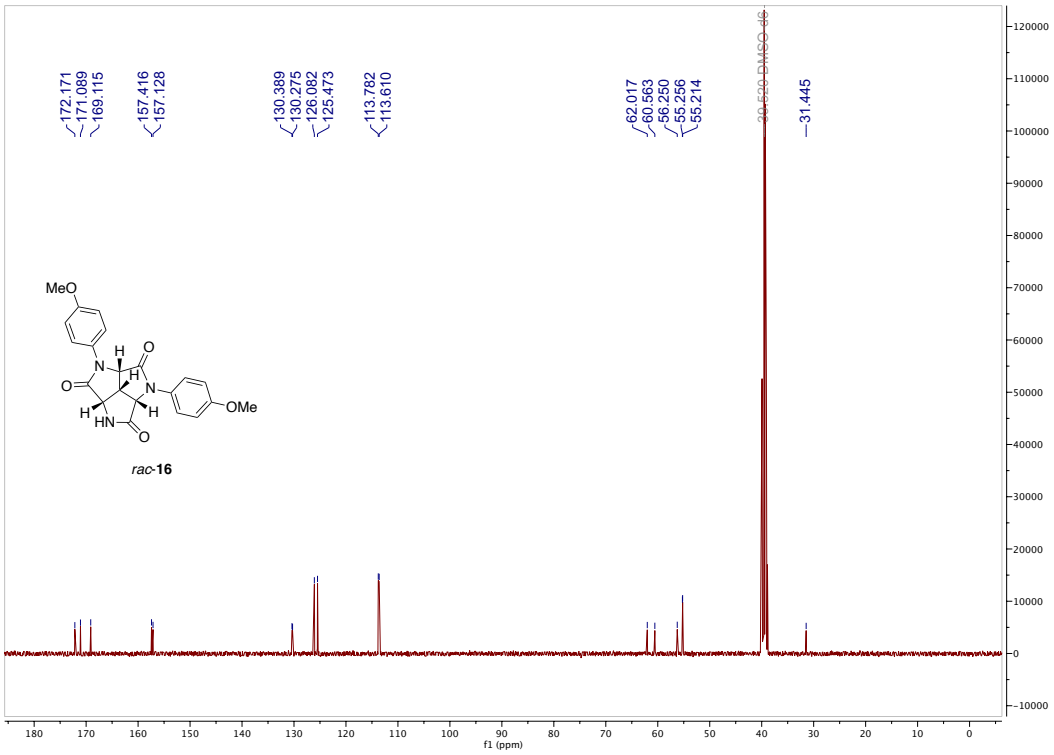


Figure S15. ^{13}C NMR spectrum (101 MHz, DMSO-d_6) of *rac*-**16**.

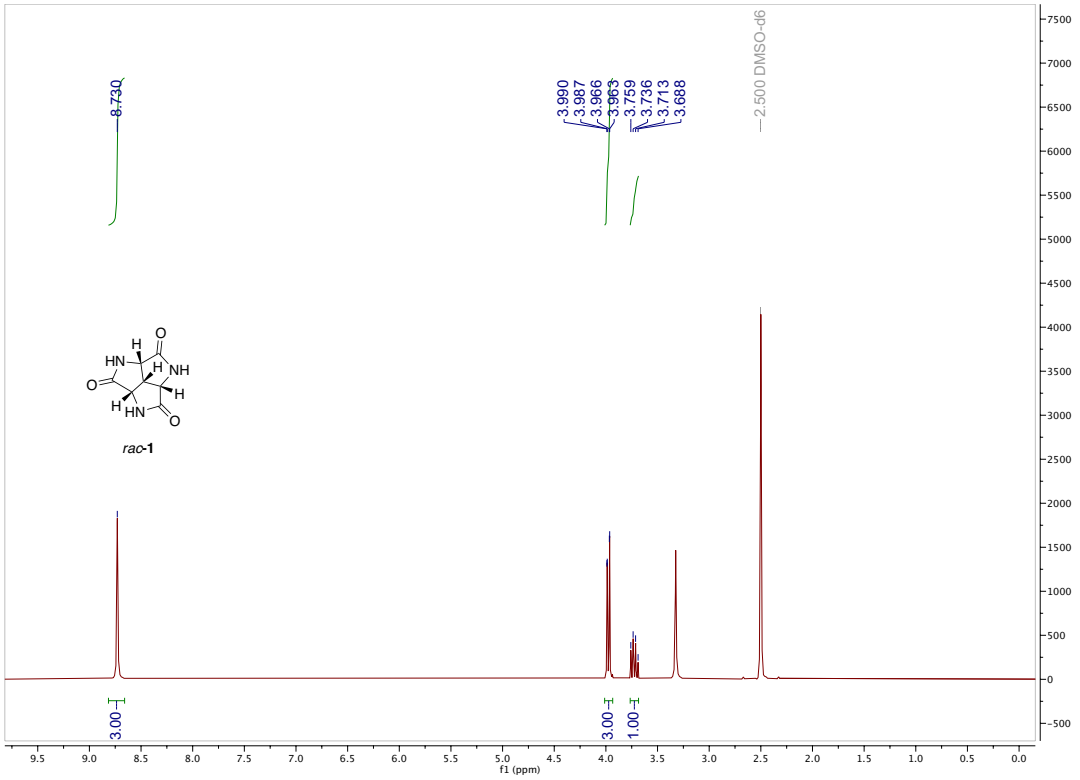


Figure S16. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of *rac*-**1**.

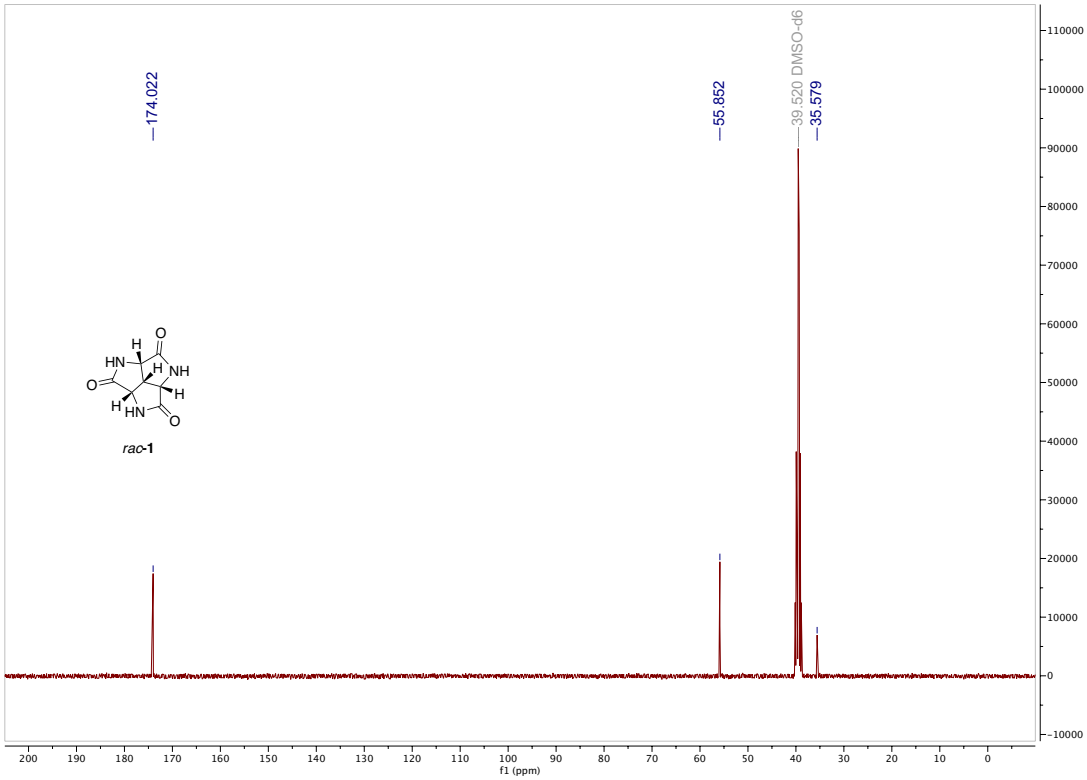


Figure S17. ^{13}C NMR spectrum (101 MHz, DMSO-d_6) of *rac*-**1**.

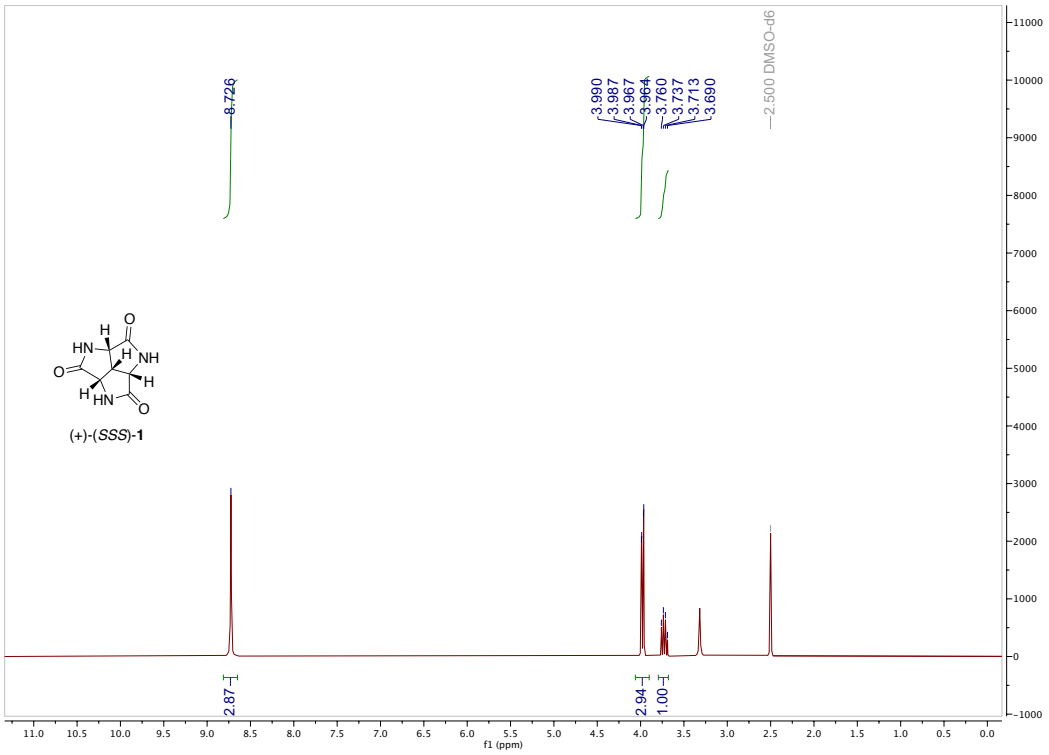


Figure S18. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of (+)-(*SSS*)-**1**.

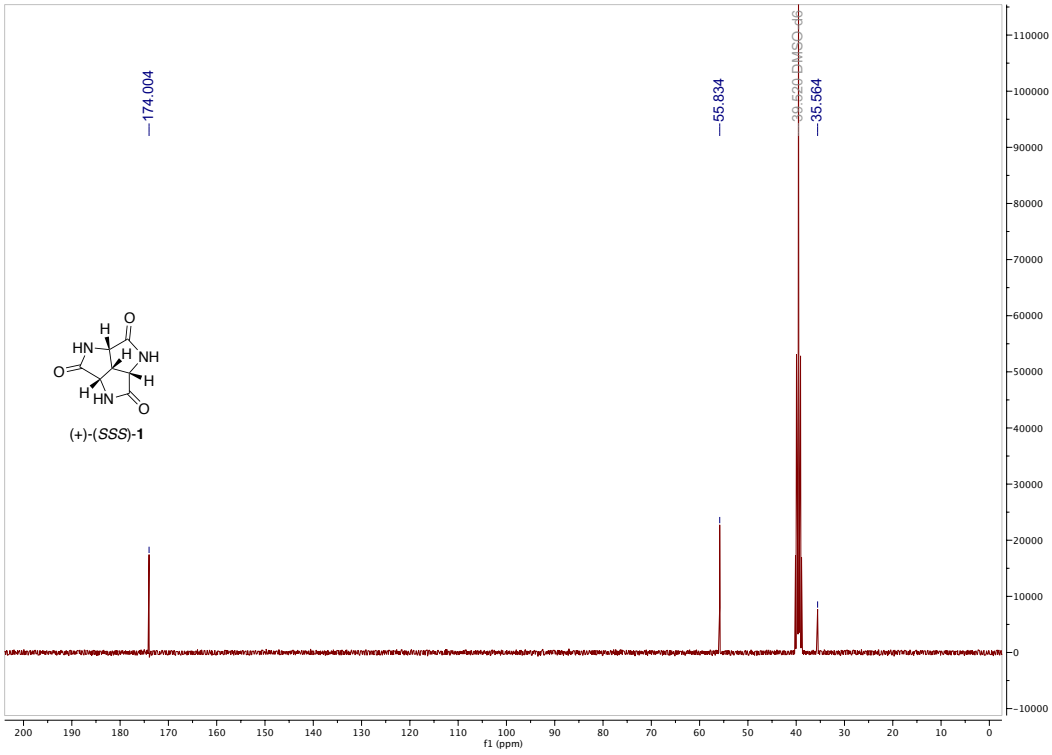


Figure S19. ^{13}C NMR spectrum (101 MHz, DMSO-d_6) of (+)-(*SSS*)-**1**.

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