## Supporting Information

for

# Efficient resolution of racemic crown-shaped cyclotriveratrylene derivatives and isolation and characterization of the intermediate saddle isomer 

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## Additional experimental details and spectra

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## 1. Synthetic procedures

## 2,7,12-Trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (3)

A suspension of phosphorus pentoxide $(9.77 \mathrm{~g}, 68.81 \mathrm{mmol})$ in 80 mL of dichloromethane was heated to $40^{\circ} \mathrm{C}$. Then, 3-methoxybenzyl alcohol (2, 18.86 g , 136.50 mmol ) was added and the mixture was refluxed for 1 hour. The mixture was filtrated and the residue extracted three times with dichloromethane. The extract was concentrated under reduced pressure and combined with the filtrate. The solution was filtrated over a 50 g pad of silica and the filtrate was concentrated under reduced pressure. After the addition of 5 mL of diethyl ether, the solution was kept overnight at $0^{\circ} \mathrm{C}$. The white precipitate was filtrated, washed with $5 \times 1 \mathrm{~mL}$ of diethyl ether and dried in high vacuum. The product ( $0.760 \mathrm{mg}, 2.11 \mathrm{mmol}, 5 \%$ ) was obtained as a white solid. The analytical data are in accordance with those reported in the literature. ${ }^{[1]}$

## 10,15-Dihydro-5H-tribenzo[a,d,g]cyclononene-2,7,12-triol ((rac)-1)

Trimethoxycyclotriveratrylene 3 ( $3.43 \mathrm{~g}, 10.77 \mathrm{mmol}$ ) was suspended in 16 mL of dry dichloromethane and cooled to $0^{\circ} \mathrm{C}$. Boron tribromide $(17.29 \mathrm{~g}, 69 \mathrm{mmol}$ as solution in dichloromethane) was slowly added and the mixture was stirred overnight at room temperature. The reaction was quenched by the addition of an ice water mixture and brought to pH 6 with a saturated aqueous sodium carbonate solution. The residue was washed with $5 \times 10 \mathrm{~mL}$ of hot water. The residue was dissolved in 12 mL of acetonitrile and treated with supersonic for 40 minutes. The formed precipitate was filtrated, washed with $5 \times 5 \mathrm{~mL}$ of acetonitrile and recrystallized from acetonitrile. The product $(2.30 \mathrm{~g}, 7.24 \mathrm{mmol}, 76 \%)$ was obtained as white solid. The analytical data are in accordance with those reported in the literature. ${ }^{[1]}$

[^0]10,15-Dihydro-5H-tribenzo[a,d,g]cyclononene-2,7,12-triol (saddle isomer, 1-S)
A solution of $71 \mathrm{mg}(\mathrm{rac})-1$ in $250 \mu \mathrm{~L}$ of EtOH was heated to $78^{\circ} \mathrm{C}$ for 1 hour. The saddle isomer is then separated via HPLC on an $(S, S)$-Whelk-O1 column as the stationary phase and $n$-hexane/ $\mathrm{EtOH} 70: 30$ as the mobile phase with a flow rate of $5.0 \mathrm{~mL} / \mathrm{min}$. The retention time of $\mathbf{1 - S}$ was 6.20 minutes.

${ }^{1} \mathrm{H}-\mathrm{NMR}\left(700,41 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}, 298 \mathrm{~K}\right.$, $\delta$ in ppm ):
6.93 (d, $3 \mathrm{H},{ }^{3} \mathrm{~J}_{2,3}=8.1 \mathrm{~Hz}, \mathrm{H}-2$ ); $6,58\left(\mathrm{~d}, 3 \mathrm{H},{ }^{3} \mathrm{~J}_{3,5}=2.5 \mathrm{~Hz}, \mathrm{H}-5\right) ; 6,57$ (dd, $3 \mathrm{H},{ }^{3} \mathrm{~J}_{5,3}=2,5$ $\mathrm{Hz},{ }^{3}{ }_{2,3}=8,1 \mathrm{~Hz}, \mathrm{H}-3$ ); 3,85 (s, $6 \mathrm{H}, \mathrm{H}-7$ ). ${ }^{* 1}$
${ }^{13} \mathrm{C}-\mathrm{NMR}\left(176,14 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}, 298 \mathrm{~K}\right.$, $\left.\delta \mathrm{im} \mathrm{ppm}\right):$
156,7 (C-4); 141,9 (C-6); 132,4 (C-2); 131,3 (C-1), 117,9 (C-5); 114,2 (C-3); 39,1 (C-7).* ${ }^{* 1}$
*1 The NMR spectra of 1-S contained impurities, especially in the aliphatic region that derived from the tubes that were used to collect the product after the HPLC separation. These impurities were not analyzed in detail.

MS (EI) m/z (Intensity\%): 318.1 (70), 211.0 (100).


Figure S1: UV-vis spectra of solutions of 1-S (left) and ( - )-( $(P)$-1 (right) in a mixture of water/acetonitrile 60:40.

## 2. HPLC separations

Chiral resolutions of 1 were performed on an analytical ultra-high pressure gradient liquid chromatography system (UHPLC) from the PLATINblue series from Knauer and a semi-preparative system from the Smartline series from Knauer.

The isolation of 1-S and the racemization experiments were performed with a Prominence system from Shimadzu. The columns that were used were an analytical CHIRALPAK IB ( $5 \mu \mathrm{~m}, 4.6 \times 250 \mathrm{~mm}$, with and without pre-column $4 \times 10 \mathrm{~mm}$ ), a semi-preparative CHIRALPAK IB ( $5 \mu \mathrm{~m}, 20 \times 250 \mathrm{~mm}$ with pre-column $30 \times 10 \mathrm{~mm}$ ), an analytical (S,S)-Whelk O1 from Regis Technologies (10 $\mu \mathrm{m}, 4 \times 300 \mathrm{~mm}$ ) and a semi-preparative (S,S)-Whelk O1 from Regis Technologies (10 $\mu \mathrm{m}, 10 \times 250 \mathrm{~mm}$ with pre-column $8 \times 30 \mathrm{~mm})$.

## Chiral resolution of (rac)-1

- 156 mg of (rac)-1 were dissolved in $1000 \mu \mathrm{~L}$ of MeOH and $400 \mu \mathrm{~L}$ of acetone.
- Separation on a semi-preparative CHIRALPAL IB column, $100 \% \mathrm{MeOH}$ as the mobile phase, flow rate: $10 \mathrm{~mL} / \mathrm{min}$, UV detection at 230 nm .
- First enantiomer was eluted after 6.88 minutes,
ee $>99 \%,[\alpha]_{D}^{20}=+272 \mathrm{~mL} \mathrm{dm}^{-1} \mathrm{~g}^{-1}(1.0 \mathrm{~g} / \mathrm{L}$, acetonitrile $),(+)-(M)-1$
ECD: $\lambda[\mathrm{nm}]\left(\Delta \varepsilon\left[\mathrm{mol} \mathrm{L}^{-1} \mathrm{~cm}^{-1}\right]\right): 208(+70) ; 222(-14) ; 233(+14) ; 245(-16) ; 275$ (+12); $294(-3)$.
- second enantiomer was eluted after 9.29 minutes, ee $>99 \%,[\alpha]_{D}^{20}=-282^{\circ} \mathrm{mL} \mathrm{dm}^{-1} \mathrm{~g}^{-1}(1.0 \mathrm{~g} / \mathrm{L}$, acetonitrile $),(-)-(P)-1$ ECD: $\lambda[\mathrm{nm}]\left(\Delta \varepsilon\left[\mathrm{mol} \mathrm{L}^{-1} \mathrm{~cm}^{-1}\right]\right): 208(-69) ; 222(+14) ; 233(-13) ; 245(+15) ; 275$ $(-12) ; 294(+3)$.


Figure S2: Chromatogram of a preparative separation of (rac)-1 on a CHIRALPAK IB column as the stationary phase and MeOH as the mobile phase.
a)

b)


Figure S3: Chromatograms of analytical UHPLC runs of resolved enantiomers (CHIRALPAK IB column as the stationary phase and MeOH as the mobile phase): a) $(+)-(M)-1, \mathrm{~b})(-)-(P)-1$ (the compound eluting at 6.2 min is not one of the enantiomers).

## Isolation of 1-S

- 71 mg were dissolved in $250 \mu \mathrm{~L}$ of EtOH and filtrated with a syringe filter.
- Separation on a semi-preparative $(S, S)$-Whelk-O1 column, n-hexane/EtOH 70:30 as the mobile phase, flow rate: $5.0 \mathrm{~mL} / \mathrm{min}$, UV detection at 254 nm .
- The retention time of 1-S was 4.20 minutes.


Figure S4: of a semi-preparative separation of (rac)-1 on an ( $S, S$ )-Whelk 01 column as the stationary phase and $n$-hexane/EtOH 70:30 as the mobile phase.

## 3. Kinetics of racemization

## Racemization experiments with (+)-1 and (-)-1

About 1 mg of (+)-1 or (-)-1 were dissolved in 1 mL of EtOH and the starting ee value was determined by HPLC. Then, the sample was placed in a preheated oil bath and heated to desired temperature. After the given time intervals, $10 \mu \mathrm{~L}$ of the solution were injected onto the CHIRALPAK IB column and the ee values were determined by integration.

Table S1: Data received from the racemization experiment starting with $(+)-(M)-\mathbf{1}$ in EtOH at $40^{\circ} \mathrm{C}$.

| time [min] | time [h] | $(+)-(\boldsymbol{M})-1[\%]$ | 1-S [\%] | $(-)-(\boldsymbol{P})-1[\%]$ |
| ---: | ---: | ---: | ---: | ---: |
| 0 | 0 | 97.37 | 0.81 | 1.82 |
| 82 | 1.37 | 96.88 | 0.85 | 2.27 |
| 1414 | 23.57 | 93.24 | 2.13 | 4.63 |
| 4179 | 69.65 | 84.53 | 2.94 | 15.33 |
| 5520 | 92.00 | 80.58 | 2.93 | 16.9 |
| 7132 | 118.87 | 77.57 | 2.85 | 19.58 |
| 8347 | 139.12 | 164.53 | 74.77 | 71.68 |
| 259.48 | 62.99 | 3.89 | 22.34 |  |
| 9872 | 289.15 | 61.18 | 2.99 | 25.31 |
| 15569 | 0.35 | 57.19 | 3.01 | 34.02 |
| 17349 |  |  | 3.08 | 35.81 |
| 21275 |  |  | 39.73 |  |

Table S2: Data received from the racemization experiment starting with $(-)-(P)-\mathbf{1}$ in EtOH at $40^{\circ} \mathrm{C}$.

| time [min] | time [h] | $(+)-(\boldsymbol{M})-\mathbf{1}[\%]$ | 1-S [\%] | $(-)-(P)-1[\%]$ |
| ---: | ---: | ---: | ---: | ---: |
| 0 | 0 | 2.12 | 1 | 96.88 |
| 1476 | 24.60 | 3.71 | 2.56 | 93.73 |
| 8821 | 147.02 | 20.17 | 3.10 | 76.73 |
| 10061 | 167.68 | 22.04 | 3.09 | 74.87 |
| 11925 | 198.75 | 25.15 | 3.06 | 71.79 |
| 15869 | 264.48 | 31.52 | 3.05 | 65.43 |
| 20170 | 336.17 | 35.11 | 3.06 | 61.83 |
| 23080 | 384.67 | 37.15 | 2.95 | 59.90 |

Table S3: Data received from the racemization experiment starting with $(+)-(M)-1$ in EtOH at $50^{\circ} \mathrm{C}$.

| time [min] | (+)-(M)-1 [\%] | 1-S [\%] | $(-)-(P)-1[\%]$ |
| :---: | :---: | :---: | :---: |
| 0 | 97.13 | 0.11 | 2.76 |
| 60 | 96.36 | 1.03 | 2.61 |
| 180 | 94.08 | 2.05 | 3.87 |
| 390 | 91.97 | 2.48 | 5.55 |
| 1500 | 80.26 | 2.89 | 16.85 |
| 1740 | 77.58 | 3.19 | 19.23 |
| 3435 | 75.35 | 3.44 | 21.2 |
| 4680 | 66.54 | 3.36 | 30.1 |

Table S4: Data received from the racemization experiment starting with $(-)-(P)-1$ in EtOH at $50^{\circ} \mathrm{C}$.

| time [h] | $(+)-(M)-\mathbf{1}[\%]$ |  | $(-)-(P)-1[\%]$ |
| ---: | :--- | :--- | :--- |
| 0 | 1.69 | 0 | 98.31 |
| 60 | 2.28 | 0.73 | 96.98 |
| 180 | 2.83 | 1.91 | 95.26 |
| 390 | 4.79 | 2.46 | 92.75 |
| 1500 | 14.27 | 3.01 | 82.72 |
| 1740 | 16.22 | 3.57 | 80.21 |
| 3435 | 18.52 | 3.41 | 78.07 |
| 4680 | 27.4 | 3.53 | 69.07 |

Table S5: Data received from the racemization experiment starting with $(+)-(M)-\mathbf{1}$ in EtOH at $60^{\circ} \mathrm{C}$.

| time [min] | $(+)-(M)-1[\%]$ |  | $(-)-(P)-1[\%]$ |
| ---: | ---: | ---: | ---: |
| 0 | 98.06 | 0.23 | 1.71 |
| 107 | 96.76 | 1.03 | 2.21 |
| 164 | 92.95 | 2.76 | 4.28 |
| 235 | 90.24 | 3.45 | 6.30 |
| 314 | 88.21 | 3.09 | 8.70 |
| 393 | 84.74 | 3.53 | 11.74 |
| 532 | 79.73 | 4.07 | 16.2 |
| 614 | 77.50 | 4.21 | 18.29 |
| 1058 | 60.47 | 3.49 | 36.04 |
| 1232 | 58.72 | 3.44 | 37.84 |
| 2540 | 50.57 | 3.81 | 45.62 |

Table S6: Data received from the racemization experiment starting with $(-)-(\mathrm{P})-1$ in EtOH at $60^{\circ} \mathrm{C}$.

| time [min] | $(+)-(M) \mathbf{- 1}[\%]$ | 1-S [\%] | $(-)-(P) \mathbf{- 1 ~ [ \% ] ~}$ |
| ---: | :--- | :--- | :--- |
| 0 | 1.45 | 0.51 | 98.04 |
| 47 | 1.95 | 2.00 | 96.05 |
| 119 | 3.07 | 2.54 | 94.39 |
| 194 | 5.20 | 3.24 | 91.56 |
| 270 | 7.11 | 3.57 | 89.32 |
| 365 | 9.95 | 4.36 | 85.69 |
| 487 | 12,86 | 3.70 | 83.44 |
| 585 | 15.60 | 3.83 | 80.57 |
| 1604 | 32.39 | 3.75 | 63.86 |
| 1885 | 35.47 | 3.77 | 60.76 |
| 3141 | 43.20 | 3.66 | 53.14 |

Table S7: Data received from the racemization experiment starting with $(+)-(M)-1$ in EtOH at $70{ }^{\circ} \mathrm{C}$

| t [min] | (+)-(M)-1 [\%] | 1-S [\%] | $(-)-(P)-1[\%]$ |
| :---: | :---: | :---: | :---: |
| 0 | 97.06 | 0.66 | 2.28 |
| 30 | 93.41 | 2.82 | 3.77 |
| 60 | 90.39 | 3.32 | 6.28 |
| 120 | 83.66 | 4.12 | 12.22 |
| 180 | 77.11 | 4.51 | 18.38 |
| 240 | 72.72 | 4.47 | 22.81 |
| 300 | 68.18 | 4.75 | 27.07 |
| 360 | 64.85 | 4.69 | 30.47 |
| 420 | 62.07 | 4.32 | 33.61 |
| 480 | 59.7 | 4.22 | 36.09 |

Table S8: Data received from the racemization experiment starting with $(-)-(P)-\mathbf{1}$ in EtOH at $70^{\circ} \mathrm{C}$

| time [min] | $(+)-(\boldsymbol{M}) \mathbf{- 1}[\%]$ |  | $(-)-(P) \mathbf{- 1}[\%]$ |
| ---: | ---: | :--- | :--- |
| 0 | 1.89 | 1.06 | 97.05 |
| 60 | 6.7 | 4.26 | 89.03 |
| 120 | 11.78 | 4.73 | 83.49 |
| 180 | 17.05 | 4.83 | 78.12 |
| 240 | 21.41 | 4.92 | 73.67 |
| 300 | 24.62 | 4.63 | 70.75 |
| 360 | 28.39 | 4.78 | 66.83 |
| 420 | 30.79 | 4.42 | 64.8 |
| 480 | 33.76 | 4.55 | 61.69 |



Figure S5: The mole fraction obtained in the racemization experiment plotted against the time, with black triangles for $(+)-(M)-\mathbf{1}$, blue triangles for $(-)-(P)-\mathbf{1}$ and red squares for 1-S. Both experiments were performed at $40^{\circ} \mathrm{C}$, left starting with $(+)-(M)-1$ and right with $(-)-(P)-1$.


Figure S6: The mole fraction obtained in the racemization experiment plotted against the time, with black triangles for $(+)-(M)-\mathbf{1}$, blue triangles for $(-)-(P)-\mathbf{1}$ and red squares for 1-S. Both experiments were performed at $50^{\circ} \mathrm{C}$, left starting with $(+)-(M)-1$ and right with $(-)-(P)-1$.


Figure S7: The mole fraction obtained in the racemization experiment plotted against the time, with black triangles for $(+)-(M)-1$, blue triangles for $(-)-(P)-1$ and red squares for 1-S. Both experiments were performed at $60^{\circ} \mathrm{C}$, left starting with $(+)-(M)-1$ and right with $(-)-(P)-1$.


Figure S8: The mole fraction obtained in the racemization experiment plotted against the time, with black triangles for $(+)-(M)-1$, blue triangles for $(-)-(P)-1$ and red squares for 1-S. Both experiments were performed at $70^{\circ} \mathrm{C}$, left starting with $(+)-(M)-1$ and right with $(-)-(P)-1$.

## Determination of the rate constants and half-lifes

The values for $k_{\text {rac }}$ were obtained by plotting the time against $\ln [((\%$ (starting enantiomer) $-50 \%) /(\%($ starting enantiomer, $t=0)-50 \%)$ ]. The rate constants $k_{r a c}$ were calculated from the slopes according to the equation:

$$
k_{r a c}=-\frac{m}{2}
$$

With: m: slope
The half-lifes $t_{1 / 2}$ were calculated according to the following equation

$$
t_{1 / 2}=\frac{\ln \frac{4}{3}}{k_{r a c}}
$$

a) $(+)-(M)-1,40^{\circ} \mathrm{C}$


$$
\begin{gathered}
k_{\mathrm{rac}}=7.722 \times 10^{-7} \mathrm{~s}^{-1} \\
t_{1 / 2}=6209.14 \mathrm{~min}
\end{gathered}
$$

b) $(-)-(P)-1,40^{\circ} \mathrm{C}$


$$
\begin{gathered}
\mathrm{K}_{\mathrm{rac}}=6.153 \times 10^{-7} \mathrm{~s}^{-1} \\
t_{1 / 2}=7792.46 \mathrm{~min}
\end{gathered}
$$

c) $(+)-(M)-1,50^{\circ} \mathrm{C}$


$$
\begin{gathered}
k_{\mathrm{rac}}=1.7376 \times 10^{-6} \mathrm{~s}^{-1} \\
t_{1 / 2}=2759.38 \mathrm{~min}
\end{gathered}
$$

d) $(-)-(P)-1,50^{\circ} \mathrm{C}$


$$
\begin{gathered}
K_{\mathrm{rac}}=1.5171 \times 10^{-6} \mathrm{~s}^{-1} \\
t_{1 / 2}=3160.44 \mathrm{~min}
\end{gathered}
$$

e) $(+)-(M)-1,60{ }^{\circ} \mathrm{C}$


$$
\begin{gathered}
k_{\mathrm{rac}}=1.4833 \times 10^{-5} \mathrm{~s}^{-1} \\
t_{1 / 2}=323.24 \mathrm{~min}
\end{gathered}
$$

f) (-)-(P)-1, $60^{\circ} \mathrm{C}$


$$
\begin{gathered}
k_{\mathrm{rac}}=7,0775 \times 10^{-6} \mathrm{~s}^{-1} \\
t_{1 / 2}=677.46 \mathrm{~min}
\end{gathered}
$$

g) $(+)-(M)-1,70^{\circ} \mathrm{C}$


$$
\begin{gathered}
k_{\mathrm{rac}}=2.758 \times 10^{-5} \mathrm{~s}^{-1} \\
t_{1 / 2}=173.85 \mathrm{~min}
\end{gathered}
$$

h) $(-)-(P)-1,70^{\circ} \mathrm{C}$


## Determination of the activation energy of racemization

The activation energy for the racemization $\Delta G^{\neq}$was obtained by plotting $\ln \left(k_{\text {rac }}\right)$ against $T^{-1}$. For $k_{\text {rac }}$ the average values for both enantiomers were used. $\Delta G^{\neq}$was calculated according to the equation:

$$
\Delta G^{\neq}=-m \cdot R
$$

With: m: slope
R: universal gas constant
Table-S 9: Values for $T-1$ and $\ln (k)$ for the Arrhenius plot.

| $\mathbf{T}[\mathbf{K}]$ | $\mathbf{1 / T}\left[\mathbf{K}^{-\mathbf{1}}\right]$ | $\ln \left(\mathbf{k}_{\text {average }}\right)$ |
| ---: | ---: | ---: |
| 313.15 | $3.19 \mathrm{E}-03$ | -14.2179 |
| 323.15 | $3.09 \mathrm{E}-03$ | -13.3286 |
| 333.15 | $3.00 \mathrm{E}-03$ | -11.4217 |
| 343.15 | $2.91 \mathrm{E}-03$ | -10.5867 |



$$
\Delta G^{\neq}=114.31 \mathrm{~kJ} \mathrm{~mol}^{-1}
$$

## 4. NMR spectra of ( $\mathbf{\pm}$ )-1 and 1-S


$60^{\circ} \angle \varepsilon-$
69 bII-
OZCLI-
OZくII-
$\begin{aligned} & 90^{\circ} \text { ZहI } \\ & \angle 0^{\circ} \text { Z\&I }\end{aligned}>$
18 ZbI
$\varepsilon \iota^{\prime} 9 \mathrm{SI}-$


The signals marked with an asterisk are due to impurities that derive from the HPLC separation.




[^0]:    1 Traoré, T.; Delacour, L.; Kotera, N.; Merer, G.; Buisson, D.-A.; Dupont, C.; Rousseau, B.Org. Process Res. Dev. 2011, 15, 435-437, DOI: 10.1021/op100260w.

