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Authors: Fatmanur Biliz and Murat Cakici

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FULL PAPER

Regioselective Synthesis of 4,7,12,15-Tetrasubstituted [2.2]Paracyclophanes: A Modular Route Involving Optical Resolution

Fatmanur Biliz[a] and Murat Cakici*[a]

[a] F. Biliz, Dr. M. Cakici
Faculty of Science, Department of Chemistry,
Ataturk University, 25240 Erzurum, Turkey
Email: mcakici@atauni.edu.tr
https://avesis.atauni.edu.tr/mcakici

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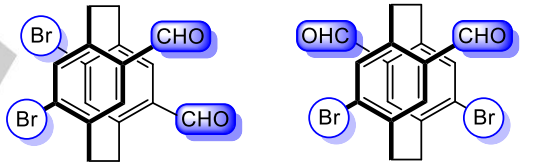
Abstract: We report a practical synthetic method for preparing bis-(*para*)-*pseudo-ortho* and bis-(*para*)-*pseudo-meta* type 4,7,12,15-tetrasubstituted [2.2]paracyclophanes. Regioselective double Rieche formylation was successfully applied to the corresponding dibromo[2.2]paracyclophanes under slightly modified conditions. Aldehydes reacted in an unknown direction with Rieche formylation agents, dichloromethyl methyl ether and titanium (IV) tetrachloride, leading to the formation of benzal chlorides. Formylated products were obtained after hydrolysis of these benzal chloride derivatives. Optical resolution was performed with the diastereomer method and (R_P)- 4,12-dibromo-7,15-diformyl[2.2]paracyclophane was successfully obtained in an enantiomerically pure form (99% *ee*). Their synthetic utility is demonstrated with some exploratory transformations to access corresponding differently functionalized tetrasubstituted [2.2]paracyclophane derivatives.

Introduction

Since the initial 1949 discovery of [2.2]paracyclophane (PCP),[1] PCP and its derivatives have received a great deal of attention in many fields of chemistry.[2] [2.2]Paracyclophane has an highly strained three-dimensional structure of two facing benzene rings that are linked in para position by a two-ethylene bridge. One of the most impressive features of substituted PCPs is their planar chirality capabilities, which offers novel opportunities in asymmetric applications not possible with traditional forms of chirality.[3]

Because of their unique structural and electronic properties, PCP derivatives have been explored for a wide range of applications, including asymmetric synthesis and materials science.[3a] In recent decades, many PCP-based planar chiral ligands and catalysts have been developed and successfully employed for various stereoselective processes.[4] Recently, the focus in [2.2]paracyclophane chemistry has shifted and studies on materials chemistry have come to the foreground.[5] [2.2]Paracyclophanes have been successfully employed as planar chiral building blocks in various functional materials including chiral metal-organic frameworks (MOFs),[6] optoelectronics,[7] circularly polarized light emitting compounds,[8] mesoporous polymers,[9] and supramolecular self-assembled structures.[10] Although there are many studies on mono- and disubstituted [2.2]paracyclophanes due to their well-known chemistry,[11] relatively little is known about tetrasubstituted [2.2]paracyclophane derivatives,[12] which have received growing attention as planar chiral scaffolds in the fields of polymer and materials chemistry.[8a]

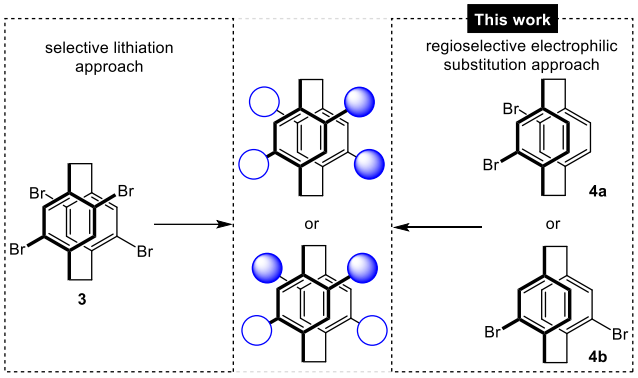
Given the many potential applications, it is important to develop new synthetic strategies for regiocontrolled synthesis[13] and optical resolution of planar chiral tetrasubstituted [2.2]paracyclophanes.[8a] In this article, we describe a practical and efficient synthetic route for bis-(*para*)-*pseudo-ortho* (**1**) and bis-(*para*)-*pseudo-meta* (**2**) type tetrasubstituted [2.2]paracyclophanes (Figure 1) from corresponding dibromo[2.2]paracyclophanes. We also examined their optical resolution and various functional group transformation to produce synthetically useful planar chiral tetrasubstituted [2.2]paracyclophane building blocks.



bis-(*para*)-*pseudo-ortho* **1** bis-(*para*)-*pseudo-meta* **2**

Figure 1. Tetrasubstituted [2.2]paracyclophane building blocks used in this study.

PCP backbone has a rigid three-dimensional structure, which makes possible a variety of different regioisomers for polysubstituted [2.2]paracyclophanes.[12b] Consequently, regiocontrolled synthesis of tetrasubstituted [2.2]paracyclophanes is often difficult. Bromo-substituted PCPs are the starting point of many types of molecular architecture for tetrasubstituted scaffolds.[14] One of the most common approaches for the synthesis of bis-(*para*)-*pseudo-ortho* and bis-(*para*)-*pseudo-meta* type tetrasubstituted [2.2]paracyclophanes is based on the selective lithiation of tetrabromo-PCP **3** followed by standard treatment with various electrophiles (Scheme 1).[15] This method can often suffer from poor regioselectivity. Regioselective electrophilic substitution of disubstituted [2.2]paracyclophanes is a more advantageous approach for obtaining tetrasubstituted [2.2]paracyclophanes.[12b] This approach has been successfully applied in the regioselective synthesis of tetrasubstituted [2.2]paracyclophane derivatives.[16]



Scheme 1. Representative synthetic routes to tetrasubstituted [2.2]paracyclophanes.

Results and Discussion

In the present work, we focused on the *para*-regioselective double formylation of dibromo[2.2]paracyclophanes. In our synthesis strategy, regioselectivity was controlled by bromine atoms on the [2.2]paracyclophane backbone. Racemic p*seudo-ortho*- (*rac*-**4a**) and *pseudo-meta*- (*rac*-**4b**) dibromo[2.2]paracyclophane precursors were prepared as described in ref.[12b, 17] (see Supporting Information for details).

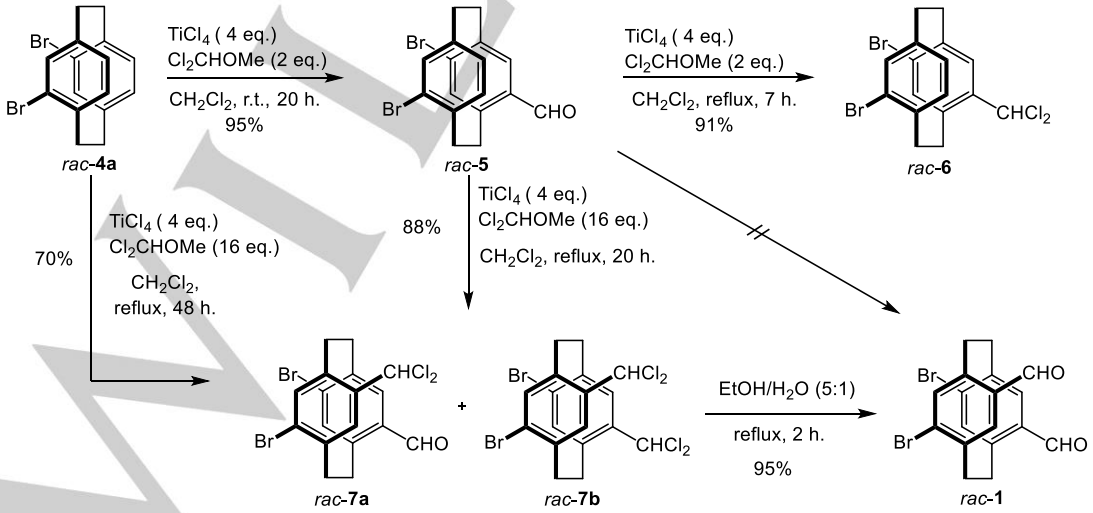
First we examined a Rieche formylation of *pseudo-ortho*-dibromo[2.2]paracyclophane (*rac*-**4a**) with various molar ratios of $TiCl_4$/dichloromethyl methyl ether (DCME) as formylating agents (Scheme 2). For molar ratio **4a**:$TiCl_4$:DCME of 1:4:2 in CH_2Cl_2 at room temperature, *para*-directed monoformylation product *rac*-**5** was obtained with a 95% yield. Many attempts were made to prepare diformylation product *rac*-**1**, but a second formyl group could not be introduced into the PCP framework with different equivalents of the formylating agents (even in excess equivalents) at room temperature. Reaction temperature was increased to 40 °C and Rieche conditions were applied for the monoformylated product *rac*-**5** by refluxing in CH_2Cl_2 with a 4:2 molar ratio of the formylating agents ($TiCl_4$/DCME). Substrate *rac*-**5** was completely consumed in 20 h; however, benzal chloride derivative *rac*-**6** was unexpectedly obtained with a 91% yield.

In the literature,[18] it has been suggested that benzal chlorides, which can be seen as side products of Rieche formylation, occur in a parallel pathway via dichloromethyl cation, a possible intermediary in the DCME-Lewis acid interaction. However, this result clearly shows that benzal chloride can also be formed from aldehyde, which is the product of the formylation reaction, through deoxygenative halogenation under Rieche conditions. Benzal chloride formation proved to be effective only when reactions were heated at 40 °C. To the best of our knowledge, there are no published reports on the conversion of aldehydes to benzal chlorides with the formylating agents $TiCl_4$/DCME. Considering the importance of developing new methods for the preparation of benzal chlorides,[19] this transformation might be synthetically valuable for direct dichloromethyl functionalization of aryl derivatives (formylation and dichlorination) or dichlorination of aldehydes.

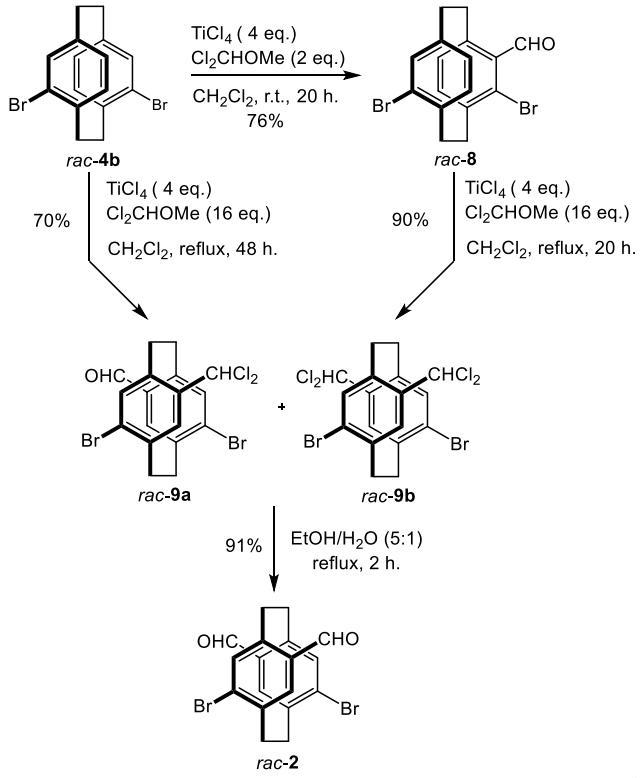
When monoformylation product *rac*-**5** was refluxed in CH_2Cl_2 with a 4:16 formylating agent ($TiCl_4$/DCME) molar ratio for 20 h, a second functionalization was achieved. However, instead of the desired diformylation product (**1**), a mixture of benzal chloride derivatives (**7**) were formed. This mixture was successfully separated by column chromatography to give *rac*-**7a** and *rac*-**7b** with yields of 31% and 57%, respectively.

It is important to note that the obtained benzal chlorides (**7**) form the skeleton of the desired diformylation product **1**. Hydrolysis of *rac*-**7a** and *rac*-**7b** as a mixture, by refluxing in aqueous ethanol (80%, v/v), afforded the desired dialdehyde *rac*-**1** at a 95% yield. In fact, *rac*-**1** was practically obtained by the initial preparation of benzal chlorides (**7**) directly from *rac*-**4a** (4 equiv of $TiCl_4$, 16 equiv of DCME, CH_2Cl_2, reflux, 48h) followed by hydrolysis of the crude reaction mixture without any purification.

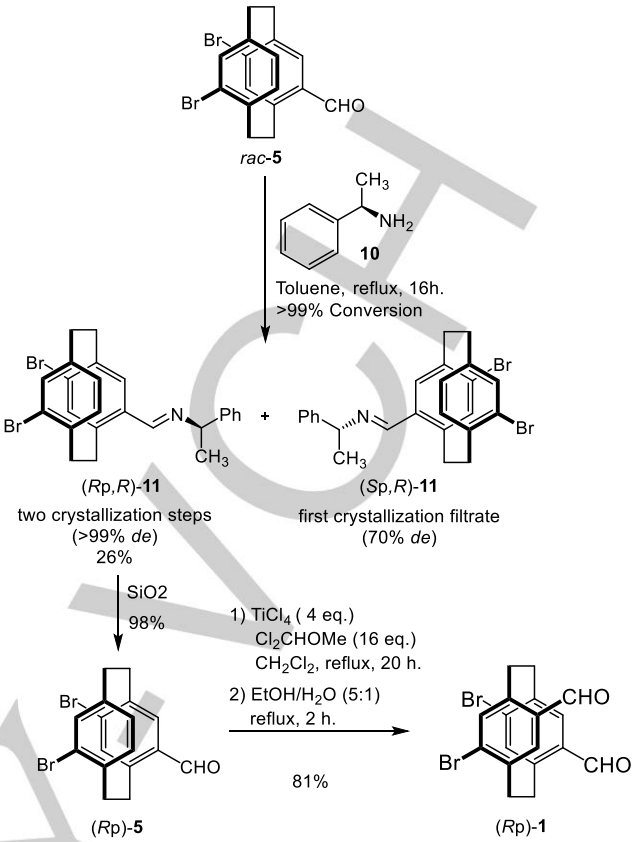
In a test reaction, *rac*-**7b** formed quantitatively from *rac*-**1** by refluxing in CH_2Cl_2 with a 4:16 formylating agent ($TiCl_4$/DCME) molar ratio for 5 h. This result supports that the $TiCl_4$/DCME pair acts as a deoxygenative halogenation agent for aldehydes as well as formylation.



Scheme 2. Synthesis of racemic12-dibromo-7,15-diformyl[2.2]paracyclophane (*rac*-**1**) by regioselective double Rieche formylation.



Scheme 3. Synthesis of bis-(*para*)-*pseudo-meta* type tetrasubstituted [2.2]paracyclophane *rac*-**2**.



Scheme 4. Optical resolution of *rac*-**5** and synthesis of enantiomerically pure (R_P)-4,12-dibromo-7,15-diformyl[2.2]paracyclophane ((R_P)-**1**).

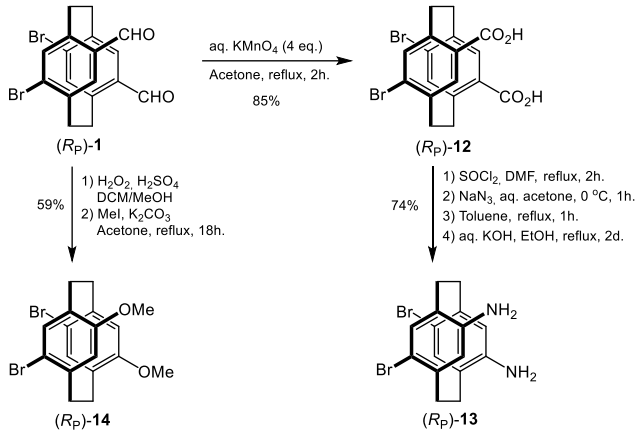
The same synthetic strategy was applied to *pseudo-meta*-dibromo[2.2]paracyclophane (*rac*-**4b**) to achieve bis-(*para*)-*pseudo-meta* type tetrasubstituted [2.2]paracyclophane *rac*-**2** (Scheme 3). First, the starting material *rac*-**4b** was treated with the formylating agents ($TiCl_4$/DCME) at a molar ratio of 4:2 at room temperature to give the corresponding monoformylation product *rac*-**8** at a 76% yield. Then tetra-functionalized PCP derivatives *rac*-**9a** and *rac*-**9b** were obtained as mixtures in different ratios from both *rac*-**4b** and *rac*-**8** under the Rieche conditions presented in Scheme 3.

The synthesis of *rac*-**2** was achieved by hydrolyzing obtained benzal chlorides (**9**), either as pure or as crude mixture, in an aqueous ethanol (80%, v/v) under reflux conditions. All compounds were confirmed by mass spectrometry and NMR spectroscopy including ^{1}H NMR and ^{13}C NMR. The spectral data were in agreement with the desired structure.

Aldehyde groups have many advantages in PCP chemistry such as mild synthesis conditions, utility in many functional group transformations, and being prepared as enantiopure through various optical resolution methods. Due to the potential asymmetric applications of tetrasubstituted PCPs, we investigated their optical resolution through aldehyde functionality. Currently, many resolution methods have been successfully applied to access enantiomerically pure PCP derivatives, including classical resolution methods,[20] chromatographic separation on chiral stationary phases,[11b, 21] and catalytic kinetic resolutions.[22] In an effort to achieve the optical resolution of *rac*-**5**, we successfully employed the classical resolution technique involving diastereomeric imine formation (Scheme 4).

Thus, *rac*-**5** was refluxed with 1.1 equivalent of (*R*)-phenylethylamine (**10**) as a chiral resolving agent in toluene for 16 h. This led to a 1:1 mixture of the two diastereomers (confirmed by ^{1}H NMR), (R_P,*R*)-**11**, and (S_P,*R*)-**11**. The fractional crystallization of the diastereomeric imine mixture **11** from hexane provided (-)-**11**, determined to be in the R_P-configuration in the following step, with >99% *de* (26% yield) after two crystallization steps. On the other hand, (S_P,*R*)-**11** was obtained from the first crystallization filtrate in ca. 70% *de*. The separation of diastereomers was followed by the characteristic imine signals at 8.30 (S_P,*R*) and 8.29 ppm (R_P,*R*) in the ^{1}H NMR spectra. Subsequently, the resulting diastereomerically pure imine (R_P,*R*)-**11** was hydrolyzed over silica gel during the chromatography and purified to generate enantiopure (R_P)-**5**. The absolute configuration of the resulting enantiomer was determined to be (R_P), by comparison of its optical rotation with that of the known (S_P)-enantiomer[23]. The enantiomeric purity of the obtained chiral product was >99%, confirmed by chiral HPLC analysis. (R_P)-**5** was then subjected to the second Rieche formylation under determined conditions to produce benzal chlorides (**7**). Hydrolyzing of the crude benzal chloride products mixture by heating in aqueous ethanol resulted in (R_P)-**1**. Unfortunately, the optical resolution of *rac*-**8** with the same method failed due to unsuccessful crystallization attempts.

Further, the synthetic utility of prepared tetrasubstituted PCPs was demonstrated by some useful functional group transformations (Scheme 5). (R_P)-**1** was oxidized into bis-carboxylic acid (R_P)-**12** by treating it with potassium permanganate at an 85% yield.



Scheme 5. Transformation of (R_P)-**1** to various synthetically useful tetrasubstituted [2.2]paracyclophane building blocks.

Bis-carboxylic acid (R_P)-**12** underwent Curtius rearrangement, resulting in the corresponding planar chiral diamine derivative. (R_P)-**13** was synthesized following established procedures: a four-step reaction sequence where only the final product needs purification. Under Dakin oxidation condition, (R_P)-**1** was converted into the corresponding dihydroxy-PCP derivative, which was isolated as methyl ether ((R_P)-**14**) at a 59% yield after treating the crude product with CH_3I and K_2CO_3.

Conclusion

In conclusion, we have developed an alternative and efficient preparation method for bis-(*para*)-*pseudo-ortho* and bis-(*para*)-*pseudo-meta* type tetrasubstituted [2.2]paracyclophanes. The corresponding dibromo[2.2]paracyclophanes underwent regioselective double Rieche formylation under the modified conditions. We found that a reaction temperature of about 40 °C is required for the second formylation. Unexpectedly, the resulting aldehyde converted into benzal chloride under Rieche conditions and a higher temperature. Further investigations are currently in progress on this new finding, which may be synthetically useful for the deoxydichlorination of aldehydes. The desired aldehyde derivatives can be easily obtained by hydrolysis of the resulting benzal chlorides. As an example of the enantiomeric separation, optical resolution of *rac*-**5** was successfully performed with the diastereomeric imine formation to give (R_P)-**5** and then (R_P)-**1** in 99% *ee*. We also demonstrated some synthetic applications of (R_P)-**1** to obtain valuable substituted PCPs. Regarding bromo-substituents, their ability to be applied for many different transformations will make **1** and **2** attractive planar chiral building blocks in PCP chemistry. Further studies on their applications in the synthesis of new functional materials are in progress in our laboratory.

Experimental Section

General

All reagents and solvents were purchased from commercial sources and used without further purification. Reactions were monitored by TLC (Thin Layer silica gel Chromatography) using Merck silica gel 60 F254 on aluminum sheets. TLC plates were visualized under UV light (254 and 366 nm). Melting points were measured using a Gallenkamp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury (400 MHz) or a Bruker Avance (400 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. Chemical shifts were expressed in parts per million (δ); multiplicities were described by the following abbreviations: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), and m (multiplet); and coupling constants values *J* were given in Hertz (Hz). High resolution mass spectra (HRMS) were obtained using an Agilent 6530 Accurate mass Q-ToF mass spectrometer. Enantiomeric excesses were determined by HPLC analysis using chiral column. Optical rotations were measured on a Bellingham + Stanley, ADP220, 589 nm spectropolarimeter in a 1 dm tube; concentrations are given in g/100 mL.

Synthesis and Characterization

4,12-Dibromo-7-formyl[2.2]paracyclophane (*rac*-5)

To a stirred solution of *pseudo-ortho*-dibromo[2.2]paracyclophane (*rac*-**4a**) (1.44 g, 3.90 mmol) in CH_2Cl_2 (16 mL) were added a solution of $TiCl_4$ (1.66 mL, 15.60 mmol) in CH_2Cl_2 (2 mL) and dichloromethyl methyl ether (706 µL, 7.80 mmol) at 0 °C. The mixture was stirred at room temperature for 20 h, poured into ice and stirred for another 1 h. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography eluting with hexane/EtOAc 9:1 to give 4,12-dibromo-7-formyl[2.2]paracyclophane (*rac*-**5**) (1.47 g, 3.70 mmol, 95%) as a white solid. R_f=0.26 (Hexane/EtOAc 19:1); m.p. 88-90°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.90 (s, 1H), 7.31 (s, 1H), 7.15 (d, *J* = 1.5 Hz, 1H), 7.03 (s, 1H), 6.44 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.41 (d, *J* = 7.9 Hz, 1H), 3.87 (dd, *J* = 13.0, 9.9 Hz, 1H), 3.52 – 3.42 (m, 2H), 3.14 – 3.01 (m, 3H), 2.95 – 2.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=191.0, 144.2, 141.2, 140.1, 138.8, 137.9, 136.3, 135.4, 134.0, 133.1, 132.9, 131.1, 126.9, 35.9, 35.5, 32.3, 30.5; HRMS (APCI-TOF) *m/z*: Calcd for $C_{17}H_{15}Br_2O$ $[M+H]^+$ 392.9484, found 392.9461.

4,12-Dibromo-7-(dichloromethyl)[2.2]paracyclophane (*rac*-6)

To a stirred solution of 4,12-dibromo-7-formyl[2.2]paracyclophane (*rac*-**5**) (0.185 g, 0.47 mmol) in CH_2Cl_2 (4 mL) were added a solution of $TiCl_4$ (200 µL, 1,88 mmol) in CH_2Cl_2 (1 mL) and dichloromethyl methyl ether (851 µL, 9.4 mmol) at 0 °C. The mixture was refluxed with stirring at 40 °C for 7 h, poured into ice and stirred for another 1 h. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography eluting with hexane/EtOAc 19:1 to give corresponding benzal chloride *rac*-**6** (0.195 g, 0.43 mmol, 91%) as a white solid. R_f=0.65 (Hexane/EtOAc 19:1); m.p. 160-162°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.24 (d, *J* = 1.9 Hz, 1H), 7.18 (s, 1H), 7.00 (s, 1H), 6.75 (s, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.44 (dd, *J* = 7.8, 1.9 Hz, 1H), 3.52 – 3.40 (m, 2H), 3.26 (dd, *J* = 14.0, 10.0 Hz, 1H), 3.15 – 3.01 (m, 3H), 2.94 – 2.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=141.4, 140.4, 138.0, 137.6, 137.2, 134.6, 133.3, 133.0, 132.7, 131.6, 128.7, 126.5, 69.5, 35.6, 35.4, 32.2, 30.2; HRMS (ESI-TOF) *m/z*: Calcd for $C_{17}H_{14}Br_2Cl$ $[M–Cl]^+$ 410.9145, found 410.9121.

Benzal chloride derivatives *rac*-7a and *rac*-7b

To a stirred solution of 4,12-dibromo-7-formyl[2.2]paracyclophane (*rac*-**5**) (0.729 g, 1.85 mmol) in CH_2Cl_2 (12 mL) were added a solution of $TiCl_4$ (789 µL, 7,40 mmol) in CH_2Cl_2 (3 mL) and dichloromethyl methyl ether (2,68 mL, 29.6 mmol) at 0 °C. The mixture was refluxed with stirring at 40 °C for 20 h, poured into ice and stirred for another 1 h. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$

and brine, dried over Na_2SO_4 and evaporated. The remaining residue was purified by column chromatography eluting with hexane/EtOAc 19:1 to give benzal chloride derivatives *rac*-**7a** (0.277 g, 0.58 mmol, 31%) and *rac*-**7b** (0.560 g, 1.05 mmol, 57%). The resulting products were used in the next step as a mixture.

Benzal chloride *rac*-**7a**: R_f=0.35 (Hexane/EtOAc 19:1); m.p. 114-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.77 (s, 1H), 7.36 (s, 1H), 7.19 – 7.14 (m, 2H), 6.87 (s, 1H), 6.71 (s, 1H), 3.96 (dd, *J* = 12.4, 9.4 Hz, 1H), 3.58 – 3.35 (m, 2H), 3.32 (dd, *J* = 14.0, 9.9 Hz, 1H), 3.16 – 2.89 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=191.6, 143.6, 140.6, 138.9, 137.8, 137.2, 136.8, 135.6, 135.5, 134.5, 132.6, 131.4, 128.8, 69.0, 34.9, 34.9, 30.7, 30.0; HRMS (APCI-TOF) *m/z*: Calcd for $C_{18}H_{14}Br_2ClO$ $[M–Cl]^+$ 438.9094, found 438.9095.

Benzal chloride *rac*-**7b**: R_f=0.54 (Hexane/EtOAc 19:1); m.p. 207-209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.32 (s, 2H), 7.01 (s, 2H), 6.60 (s, 2H), 3.49 – 3.38 (m, 4H), 3.13 (ddd, *J* = 13.5, 9.9, 7.7 Hz, 2H), 2.97 (ddd, *J* = 13.5, 9.9, 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=138.9, 138.4, 136.5, 134.9, 130.9, 128.5, 69.6, 34.9, 30.2; HRMS (APCI-TOF) *m/z*: Calcd for $C_{18}H_{14}Br_2Cl_3$ $[M–Cl]^+$ 492.8522, found 492.8517.

4,12-Dibromo-7,15-diformyl[2.2]paracyclophane (*rac*-1)

The mixture of *rac*-**7a** and *rac*-**7b** (0.837 g, 1.63 mmol) from previous step was dissolved in 25 mL of EtOH/H_2O (5:1) and the resulting solution was refluxed for 2 h. After completion of the reaction (by monitoring TLC), the solvent was evaporated under reduced pressure. The residue was taken up in CH_2Cl_2 (20mL) and the solution washed with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (20mL) and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified on silica gel column using hexane/EtOAc, (9:1) to afford 4,12-dibromo-7,15-formyl[2.2]paracyclophane (*rac*-**1**) (0.654 g, 1.55 mmol, 95%) as a white solid. R_f=0.15 (Hexane/EtOAc 19:1); m.p. 202-205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.79 (s, 2H), 7.27 (s, 2H), 6.88 (s, 2H), 4.00 – 3.87 (m, 2H), 3.55 – 3.41 (m, 2H), 3.13 – 2.94 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=191.4, 143.6, 140.3, 137.6, 136.1, 135.6, 133.2, 35.2, 30.7; HRMS (APCI-TOF) *m/z*: Calcd for $C_{18}H_{15}Br_2O_2$ $[M+H]^+$ 420.9433, found 420.9420.

4,15-Dibromo-7-formyl[2.2]paracyclophane (*rac*-8)

To a stirred solution of *pseudo-meta*-dibromo[2.2]paracyclophane (*rac*-**4b**) (1.15 g, 3.14 mmol) in CH_2Cl_2 (16 mL) were added a solution of $TiCl_4$ (1.34 mL, 12.56 mmol) in CH_2Cl_2 (2 mL) and dichloromethyl methyl ether (568 µL, 6.28 mmol) at 0 °C. The mixture was stirred at room temperature for 20 h, poured into ice and stirred for another 1 h. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography eluting with hexane/EtOAc 4:1 to give 4,15-dibromo-7-formyl[2.2]paracyclophane (*rac*-**8**) (0.940 g, 2.39 mmol, 76%) as a white solid. R_f=0.42 (Hexane/EtOAc 19:1); m.p. 135-138°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.87 (s, 1H), 7.60 (s, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.72 (s, 1H), 6.52 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.48 (d, *J* = 1.8 Hz, 1H), 4.07 (dd, *J* = 13.0, 10.0 Hz, 1H), 3.40 – 3.30 (m, 2H), 3.23 – 3.13 (m, 2H), 3.13 – 3.02 (m, 1H), 2.95 (ddd, *J* = 13.0, 10.1, 7.1 Hz, 1H), 2.76 (ddd, *J* = 13.0, 10.1, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=191.7, 143.5, 141.5, 140.2, 139.9, 138.8, 136.0, 135.5, 135.0, 133.8, 130.8, 130.7, 127.4, 34.0, 33.4, 33.4, 33.0; HRMS (APCI-TOF) *m/z*: Calcd for $C_{17}H_{15}Br_2O$ $[M+H]^+$ 392.9484, found 392.9481.

Benzal chloride derivatives *rac*-9a and *rac*-9b

To a stirred solution of 4,15-dibromo-7-formyl[2.2]paracyclophane (*rac*-**8**) (0.197 g, 0.50 mmol) in CH_2Cl_2 (5 mL) were added a solution of $TiCl_4$ (213 µL, 2,00 mmol) in CH_2Cl_2 (1 mL) and dichloromethyl methyl ether (724 µL, 8.00 mmol) at 0 °C. The mixture was refluxed with stirring at 40 °C for 20 h, poured into ice and stirred for another 1 h. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. The remaining residue was purified by column chromatography eluting with hexane/EtOAc 39:1 to give benzal chloride derivatives *rac*- **9a** (0.029 g, 0.06 mmol, 12%) and *rac*-**9b** (0.207 g, 0.39 mmol, 78%). The resulting products were used in the next step as a mixture.

Benzal chloride *rac*-**9a**: R_f=0.31 (Hexane/EtOAc 19:1); m.p. 139-141°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.88 (s, 1H), 7.66 (s, 1H), 7.44 (s, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 6.44 (s, 1H), 4.08 (dd, *J* = 12.9, 9.7 Hz, 1H), 3.46 – 3.30 (m, 3H), 3.27 – 3.17 (m, 1H), 3.15 – 3.06 (m, 1H), 3.03 – 2.93 (m, 1H), 2.88 – 2.078 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=191.9, 142.2, 140.1, 140.0, 137.8, 137.5, 137.4, 137.1, 135.4, 135.3, 133.4, 129.1, 128.9, 68.8, 33.1, 32.8, 32.7, 31.8; HRMS (APCI-TOF) *m/z*: Calcd for $C_{18}H_{15}Br_2Cl_2O$ $[M+H]^+$ 474.8861 found 474.8860.

Benzal chloride *rac*-**9b**: R_f=0.44 (Hexane/EtOAc 19:1); m.p. 168-170°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.51 (s, 2H), 6.81 (s, 2H), 6.73 (s, 2H), 3.52 – 3.40 (m, 2H), 3.39 – 3.27 (m, 2H), 3.23 – 3.10 (m, 2H), 2.99 – 2.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=140.2, 136.6, 136.5, 136.3, 129.1, 128.8, 69.1, 32.6, 32.1; HRMS (ESI-TOF) *m/z*: Calcd for $C_{18}H_{14}Br_2Cl_3$ $[M–Cl]^+$ 492.8522, found 492.8515.

4,15-Dibromo-7,12-diformyl[2.2]paracyclophane (*rac*-2)

The mixture of *rac*-**9a** and *rac*-**9b** (0.236 g, 0.45 mmol) from previous step was dissolved in 15 mL of EtOH/H_2O (5:1) and the resulting solution was refluxed for 2 h. After completion of the reaction (by monitoring TLC), the solvent was evaporated under reduced pressure. The residue was taken up in CH_2Cl_2 (20mL) and the solution washed with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (20mL) and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified on silica gel column using hexane/EtOAc, (9:1) to afford 4,12-dibromo-7,15-formyl[2.2]paracyclophane (*rac*-**2**) (0.172 g, 0.41 mmol, 91%) as a white solid. R_f=0.24 (Hexane/EtOAc 19:1); m.p. 177-179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.90 (s, 2H), 7.58 (s, 2H), 6.60 (s, 2H), 4.11 – 3.98 (m, 2H), 3.45 – 3.32 (m, 2H), 3.24 – 3.10 (m, 2H), 2.97 – 2.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=191.4, 143.8, 139.9, 138.6, 135.5, 134.7, 133.6, 32.9, 32.8; HRMS (APCI-TOF) *m/z*: Calcd for $C_{18}H_{15}Br_2O_2$ $[M+H]^+$ 420.9433, found 420.9431.

Optical Resolution of racemic 4,12-dibromo-7-formyl[2.2]paracyclophane (*rac*-5)

rac-4,12-dibromo-7-formyl[2.2]paracyclophane (*rac*-**5**) (1.48 g, 3.76 mmol) and (*R*)-phenylethylamine (**10**) (5.02 g, 4.14 mmol) were heated under reflux in toluene (50 mL). The progress of the reaction was monitored by ^{1}H NMR spectroscopy. After 16 h, the solvent was evaporated and the crude product **11** (mixture of diastereoisomers) recrystallized twice from hexane (10 mL, then 5 mL) giving imine (R_P,*R*)-**11** (de: >99%, calculated by ^{1}H NMR considering the resonance at 8.30 (S_P,*R*) and 8.29 (R_P,*R*) ppm or 7.06 (S_P,*R*) and 7.01 (R_P,*R*) ppm). Yield: 0.49 g (0.99 mmol, 26%); (R_P,*R*)-**11**; m.p. 135-138°C; $[\alpha]_D^{20}$= –287 (*c*=0.54, in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.29 (s, 1H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.23 (m, 1H), 7.21 (s, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.01 (s, 1H), 6.48 – 6.36 (m, 2H), 4.55 (q, *J* = 6.6 Hz, 1H), 3.73 (dd, *J* = 13.2, 9.8 Hz, 1H), 3.46 – 3.29 (m, 2H), 3.12 – 2.96 (m, 3H), 2.88 – 2.76 (m, 1H), 2.72 – 2.59 (m, 1H), 1.66 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=157.7, 145.1, 141.8, 141.3, 139.2, 138.8, 136.1, 135.4, 134.6, 133.0, 131.2, 128.7, 128.6, 127.1, 126.8, 126.7, 70.8, 35.6, 35.3, 32.4, 30.7, 25.1.

(S_P,*R*)-**11** was obtained from the first crystallization filtrate with about 70% *de*

(R_P)-4,12-Dibromo-7-formyl[2.2]paracyclophane ((R_P)-5)

(R_P,*R*)-**11** (0.49 g, 0.99 mmol) was hydrolyzed and separated on silica gel column by eluting with CH_2Cl_2. (R_P)-4,12-Dibromo-7-formyl[2.2]paracyclophane ((R_P)-**5**) (382 mg, 0.97 mmol, 98%) was

obtained as a white solid. $[\alpha]_D^{20}$= –193 (*c*=0.58, in CH_2Cl_2); *ee*: >99%; HPLC conditions: 9.8 min (*R*), 10.8 min (*S*). Chiralcel OD-H column, *n*-hexane/*i*-PrOH 95:05, 1 mL/min flow rate, 254 nm.

(R_P)-4,12-Dibromo-7,15-diformyl[2.2]paracyclophane ((R_P)-1)

(R_P)-**1** was prepared from (R_P)-**5** by following the same procedure as described in the synthesis of (*rac*)-**5**. $[\alpha]_D^{20}$= –157 (*c* 1.0, CH_2Cl_2). All the spectral data were in agreement with (*rac*)-**5**

(R_P)-4,12-Dibromo-7,15-dicarboxy[2.2]paracyclophane ((R_P)-1)

To a stirred solution of (R_P)-4,12-dibromo-7,15-formyl[2.2]paracyclophane ((R_P)-**1**) (0.296 g, 0.70 mmol) in acetone (3 mL), a solution of potassium permanganate (0.553 g, 3,50 mmol) in H_2O (3 mL) was added dropwise and the mixture was refluxed for 2 h. After cooling to room temperature, the suspension was filtered and washed with water (3 mL). Aqueous layer was acidified to pH 1 by the addition of hydrochloric acid. The precipitate was separated by filtration and after washing with CH_2Cl_2 (1 mL) and water (3 mL) dried on air to yield pure (R_P)-4,12-dibromo-7,15-dicarboxy[2.2]paracyclophane ((R_P)-**12**) (0.274 g, 0.60 mmol, 85%) as a white solid. m.p. 186-187°C; $[\alpha]_D^{20}$= +167 (*c*=0.3, in DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ=12.91 (bs, 2H), 7.18 (s, 2H), 7.15 (s, 2H), 3.82 (dd, *J* = 12.1, 9.4 Hz, 2H), 3.24 (dd, *J* = 12.8, 9.2 Hz, 2H), 3.10 – 2.97 (m, 2H), 2.97 – 2.85 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ=167.0, 143.4, 139.0, 135.1, 134.5, 131.0, 129.9, 34.3, 32.0; HRMS (ESI-TOF) *m/z*: Calcd for $C_{18}H_{14}Br_2NaO_4$ $[M+Na]^+$ 474.9151, found 474.9144.

(R_P)-4,12-Diamino-7,15-dibromo[2.2]paracyclophane ((R_P)-13)

(R_P)-4,12-dibromo-7,15-dicarboxy[2.2]paracyclophane ((R_P)-**12**) (0.275 g 0.585 mmol) was dissolved in 5 mL $SOCl_2$. Two drops of DMF were added, then the mixture was refluxed for 1 h. Excess $SOCl_2$ was removed under reduced pressure to give the corresponding acyl chloride (0.285 g, 0.580 mmol, 99%). Without any further purification the corresponding acyl chloride was used in the next step. The crude acyl chloride was dissolved in acetone (20 mL) and the mixture was cooled to 0 °C. To this cooled mixture was added a solution of NaN_3 in H_2O (10mL) dropwise and stirred at 0 °C for 1 h. The reaction mixture was then diluted with H_2O (10mL) and extracted with diethyl ether (3x20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The corresponding acyl azide (0.277 g, 0.550 mmol, 95%) was obtained as a white solid and used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.24 (s, 2H), 7.17 (s, 2H), 3.99 – 3.92 (m, 2H), 3.46 – 3.31 (m, 2H), 3.13 – 2.93 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=172.0, 144.7, 140.0, 135.8, 135.1, 132.9, 130.3, 34.8, 32.4. Toluene (8 mL) was added to the obtained acyl azide, and the solution was refluxed for 1 h. The solvent was evaporated under reduced pressure and the almost pure isocyanate (0.237 g, 0.530 mmol, 96%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.18 (s, 2H), 6.54 (s, 2H), 3.36 – 3.29 (m, 2H), 3.17 – 3.10 (m, 2H), 2.95 – 2.82 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=140.7, 135.5, 135.0, 133.3, 128.6, 128.5, 123.6, 33.8, 29.6. The obtained isocyanate was dissolved in EtOH (15 mL) and the solution was refluxed for 2 h. Aqueous potassium hydroxide solution (5 mL, 20%) was added and further continued reflux for 45 h. The reaction mixture was cooled to room temperature and poured into 30 mL of ice-cold potassium hydroxide solution (20%). The precipitated off-white solid was collected by filtration, washed with water and air-dried to give (R_P)-4,12-diamino-7,15-dibromo[2.2]paracyclophane ((R_P)-**13**) (0.170 g, 0.430 mmol, 81%). The overall yield for the four-step sequence was 74%. m.p. 151-153°C; $[\alpha]_D^{20}$= –82 (*c*=0.33, in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ=6.98 (s, 2H), 6.25 (s, 2H), 3.44 (bs, 4H), 3.21 – 3.05 (m, 2H), 2.94 – 2.74 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=144.6, 139.5, 134.7, 125.8, 118.4, 115.3, 32.7, 29.1; HRMS (ESI-TOF) *m/z*: Calcd for $C_{16}H_{17}Br_2N_2$ $[M+H]^+$ 394.9753, found 394.9745.

(R_P)-4,12-Dibromo-7,15-dimethoxy[2.2]paracyclophane ((R_P)-14)

To a stirred solution of (R_P)-**1** (42 mg, 0.1 mmol) in 3 mL of CH_2Cl_2/MeOH (1:1) were added concentrated H_2SO_4 (1 drop) and H_2O_2 (30 µL, 50% in water, 0.5 mmol). After stirring at room temperature for 4 d, the reaction mixture was concentrated in vacuo, diluted with CH_2Cl_2 (10 mL) and washed with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (10mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting dihydroxy[2.2]paracyclophane derivative was used for the next reaction without purification. The crude product was dissolved in acetone (5 mL), and K_2CO_3 (276 mg, 2 mmol) and iodomethane (70 mg, 0.5 mmol) were added to the solution. The reaction mixture was stirred at reflux temperature under N_2 atmosphere for 20 h. The cooled mixture was filtrated, and the filtrate was evaporated under reduced pressure. The residue was purified on silica gel column using hexane/EtOAc, (9:1) to afford (R_P)-**14** (25 mg, 0.059 mmol, 59%) as a white solid. R_f=0.45 (Hexane/EtOAc 19:1); m.p. 127-129 °C; $[\alpha]_D^{20}$= –45 (*c*=0.5, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.07 (s, 2H), 6.16 (s, 2H), 3.69 (s, 6H), 3.29 – 3.11 (m, 4H), 2.88 – 2.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=158.0, 141.3, 134.7, 128.6, 117.6, 116.0, 55.7, 34.3, 28.1; HRMS (APCI-TOF) *m/z*: Calcd for $C_{18}H_{19}Br_2O_2$ $[M+H]^+$ 424.9746, found 424.9734.

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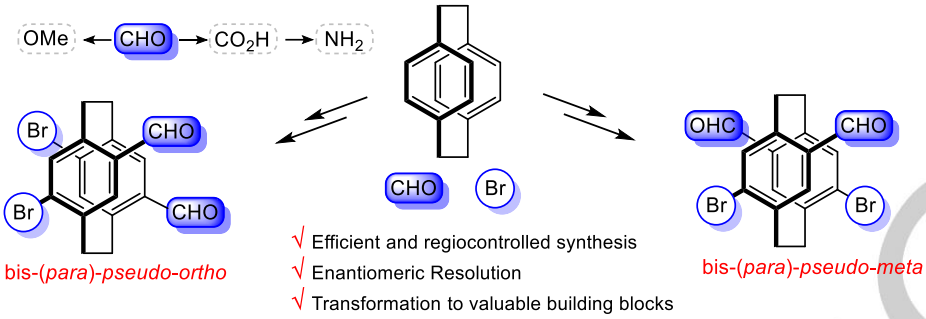

Regioselective preparation of tetrasubstituted [2.2]paracyclophanes, which are useful planar chiral building blocks for various functional materials, is a difficult task. We report a new efficient synthetic route for obtaining bis-(*para*)-*pseudo-ortho* and bis-(*para*)-*pseudo-meta* type tetrasubstituted [2.2]paracyclophanes. We evaluate the optical resolution and some useful transformations.