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SHORT COMMUNICATION

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Synthesis of Bromo-Substituted 4-Hydroxy[2.2]paracyclophanes and [2.2]Paracyclophane-4,7-quinones as Versatile Chiral Building Blocks

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Approaches to a number of bromo-substituted derivatives of 4-hydroxy[2.2]paracyclophane, including the regioselective mono- and dibromination of this phenol, were investigated. The applicability of the regioisomeric monobromo-substituted phenols for the synthesis of substituted [2.2]paracyclophane-4,7-quinones through a one-pot diazonium coupling/reduction/oxidation sequence was demonstrated. The compounds obtained possess various substitution patterns and could be used for the synthesis of a wide range of [2.2]paracyclophane derivatives by transformation of the bromine, hydroxy, and quinoid fragments.

Introduction

The success in using [2.2]paracyclophane derivatives as chiral promoters in various stereoselective processes[1] and as building blocks in polymer and materials science[2] has prompted chemists to seek out novel compounds possessing definitive structural features.[3] Owing to the unique rigidity of the [2.2]paracyclophane scaffold and the variety of possible patterns (mono- and polysubstituted aromatic rings, aliphatic bridges, and their combinations), one can govern the parameters of the molecules, including the number of attached functional groups, their electronic and steric features, relative orientation, rigid or flexible connection, to provide a certain distance between them. Directing effects of various substituents uncovered by Cram in the 1960s[4] and the extension of this early chemistry to new approaches[5] has permitted the controlled synthesis of a multitude of mono- and polysubstituted achiral and planar/central chiral [2.2]paracyclophanes. This chemistry in conjunction with the development of new resolution techniques[6] has allowed the number of useful ligands and building blocks in enantiomerically pure form to grow continually.

The conversion of bromo substituents attached to a [2.2]-paracyclophane moiety is the foundation of most syntheses providing introduction of various functionalities.[1,3a] A number of bromo- and polybromo-substituted phenols and diphenols **1**–**9** have previously been reported in either racemic or enantiomerically enriched form[5e,7] (Figure 1). In the course of our investigations[8] we required several regioisomeric monobromo-substituted phenols. To our surprise, *para* regioisomer **5** had not been reported, even though its methyl ether was previously synthesized by *para*-regioselective bromination of 4-methoxy[2.2]paracyclo-

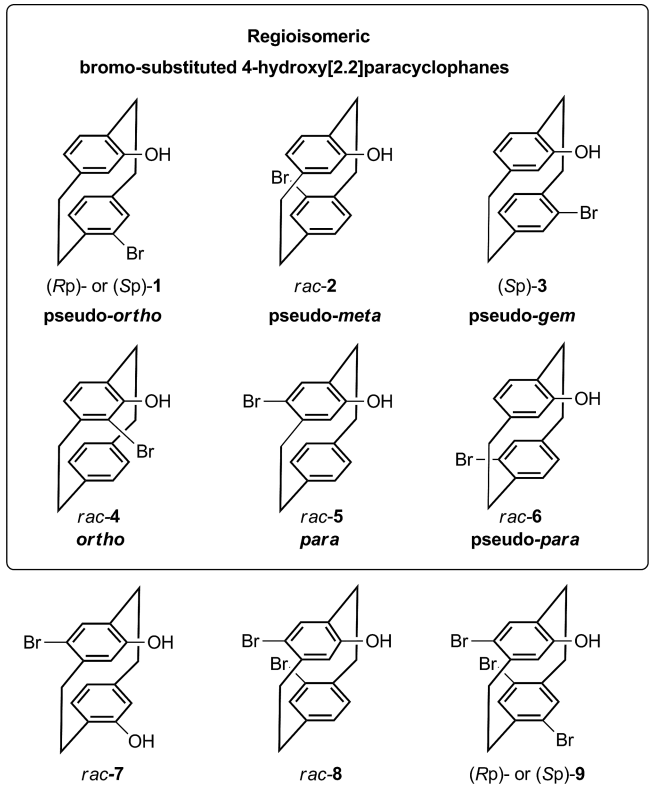

Figure 1. Bromo-substituted phenols of [2.2]paracyclophane series.

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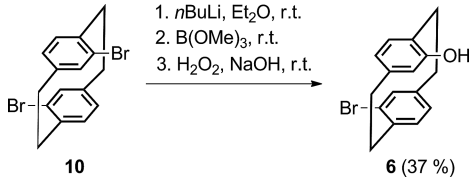
phane.[9] Additionally, whereas pseudo-*para* derivative **6** has been reported by Cram,[7e] its synthesis was not efficient.

In this communication we would like to disclose the synthesis of new members of the bromophenol series and to demonstrate the reactivity of several regioisomeric monobromo-substituted 4-hydroxy[2.2]paracyclophanes in the synthesis of novel substituted quinones.

Results and Discussion

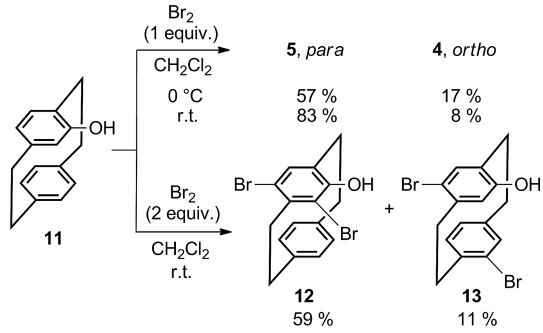
There is no general approach to the synthesis of all the possible regioisomeric monobromo-substituted 4-hydroxy-[2.2]paracyclophanes (Figure 1). The synthesis of 12-bromo-4-hydroxy[2.2]paracyclophane and 15-bromo-4-hydroxy[2.2]paracyclophane (pseudo-*ortho* **1** and pseudo-*meta* **2**) is based on the selective low-temperature[7a] or room-temperature monolithiation[7c] of the respective regioisomeric dibromides followed by standard treatment with $B(OMe)_3$ and oxidation of the intermediate boronic esters with H_2O_2/NaOH. 13-Bromo-4-hydroxy[2.2]paracyclophane (pseudo-*gem* **3**) is obtainable through a multistep synthesis that culminates in converting the amino group of the respective bromo-substituted amine into a hydroxy group.[7d] 5-Bromo-4-hydroxy[2.2]paracyclophane (*ortho*-**4**) can be prepared in several steps from the product of the palladium-directed halogenation of imines.[5e] To complete a series of preparatively available regioisomeric monobromo-substituted 4-hydroxy[2.2]paracyclophanes **1**–**6**, we turned our attention to the synthesis of **5** and **6**.

16-Bromo-4-hydroxy[2.2]paracyclophane (pseudo-*para* **6**) was obtained[7e] together with three other products upon treatment of dibromide **10**[4a,10] with potassium *tert*-butoxide in DMSO followed by acidic ether hydrolysis. The synthetic procedure was laborious and **7** was not fully characterized. On the other hand, it is known that the reaction of **10** with *n*BuLi in Et_2O at room temperature occurs with exchange of only one bromine atom by lithium.[11] To improve the preparation of **6**, we monolithiated **10**, which was followed by introduction of a hydroxy group by a standard procedure (Scheme 1). The low yield of **6** can be explained by the poor solubility of starting material **10** and the increased solubility of the monolithiated species, which results in a further, undesired, dilithiation reaction. The mixture of lithio derivatives after the workup gave rise to target **6** together with 4-hydroxy[2.2]paracyclophane (**11**) and parent [2.2]paracyclophane (both well detectable by TLC) as products of the partial and full hydrolysis of the dilithio derivative.



Scheme 1. Synthesis of 16-bromo-4-hydroxy[2.2]paracyclophane (**6**).

To the best of our knowledge, only one example of the electrophilic aromatic substitution of phenol **11** has been described.[12] The phthalimide sulfenylation of **11** produced a mixture of *ortho*- and *para*-substituted phenols in a 3:2 ratio or the single *ortho*,*para*-disubstituted phenol, depending on the amount of the reagent used. We investigated the mono- and dibromination of phenol **11** as a possible route for the synthesis of the novel derivatives (Scheme 2).



Scheme 2. Mono- and dibromination of 4-hydroxy[2.2]paracyclophane **1**.

Reaction of **11** with an equimolar amount of Br_2 at 0 °C produced a mixture of *para* and *ortho* isomers {novel 7-bromo-4-hydroxy[2.2]paracyclophane (**5**) and known **4**}, which were separated by preparative chromatography to give yields of 57 and 17%, respectively. Performing the bromination at room temperature allowed us to increase the *para* regioselectivity, which resulted in the formation of **5** in a yield of 83%, whereas the yield of **4** was low. The latter compound could not be purified by chromatography or recrystallization because in the ^1H NMR spectrum of the TLC-pure samples we always observed a considerable amount of the admixture product of presumable further bromination, which has a very close R_f, and it could not be removed by crystallization.

The reaction of **11** with 2 equivalents of Br_2 proceeded smoothly at room temperature to produce a mixture of regioisomeric dibromo-substituted phenols **12** and **13** (Scheme 2) that were easily separable by preparative chromatography. The structure of **12** was supported by X-ray diffraction analysis (Figure 2). Compound **12** is a rare example of a [2.2]paracyclophane that has three substituents on a single ring. This result is analogous to the chemistry of *N*-thiophthalamide.[12] Earlier, we described a tribromo-substituted [2.2]paracyclophane with all bromine atoms in one aromatic rings that was formed in a trace amount only.[10] Dialkyl- and diallylphenols of such a type were obtained as minor products (4–22%) in the acid-catalyzed dehydration of *cis*-4,7-disubstituted 4,7-dihydro-4,7-dihydroxy[2.2]paracyclophanes.[13] If one considers the known directing effects in the substitution reactions of [2.2]paracyclophane derivatives[4a,10] then it is likely that major product **12** arises from both **5** and **4** by further bromination of the substituted aromatic ring (*ortho* and *para* outcome of the second substituent with respect to the hydroxy group, Figure 1). Minor phenol **13** is the product of substitution of the lower ring. The regiochemistry of this reaction is driven by steric hindrance and not by electronics, so bromination occurs at the most accessible position. The

high yield of **12** is probably the result of the highly activating effect of the hydroxy group. Similar effects were observed during the bis-sulfenylation of **11**, which was proven to be the unique example of a double substitution product in a series of approximately 50 phenols. Its formation was attributed to stereoelectronic effects of the [2.2]paracyclophane moiety, which allowed the withdrawing effect of the first thiophthalimide group to be overcome.[12]

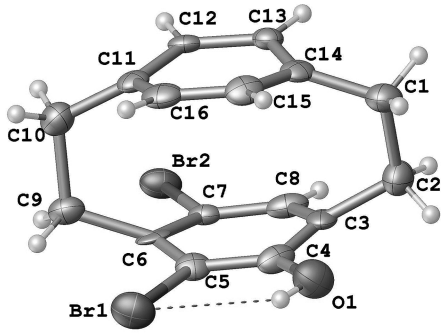


Figure 2. Molecular view of 5,7-dibromo-4-hydroxy[2.2]paracyclophane (**12**); thermal ellipsoids given with $p = 50\%$.

[2.2]Paracyclophane-derived quinones, quinhydrones, and their esters were traditionally used as attractive models to investigate the dependence of donor–acceptor (D-A) interactions with respect to the mutual arrangement of the D and A substituents.[14] Multistereogenic bis-bifunctional ligands **15**, obtainable by stereoselective addition of organolithium compounds to enantiomers of [2.2]paracyclophane-4,7-quinone (**14**),[15] were applied as chiral ligands in the asymmetric diethylzinc addition to aldehydes.[15b] Recently, the respective *para*-ditriflate obtained from (*Sp*)-**14** was found to be a suitable precursor for the synthesis of diaryl derivatives (*Sp*)-**16** by double Suzuki coupling[16] (Figure 3).

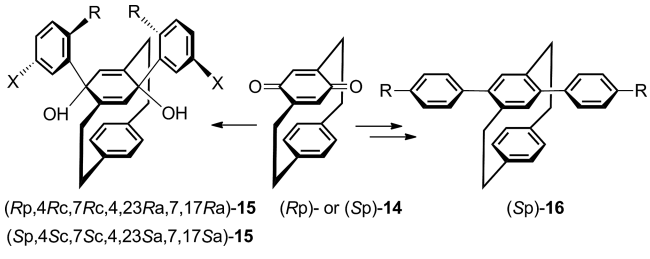
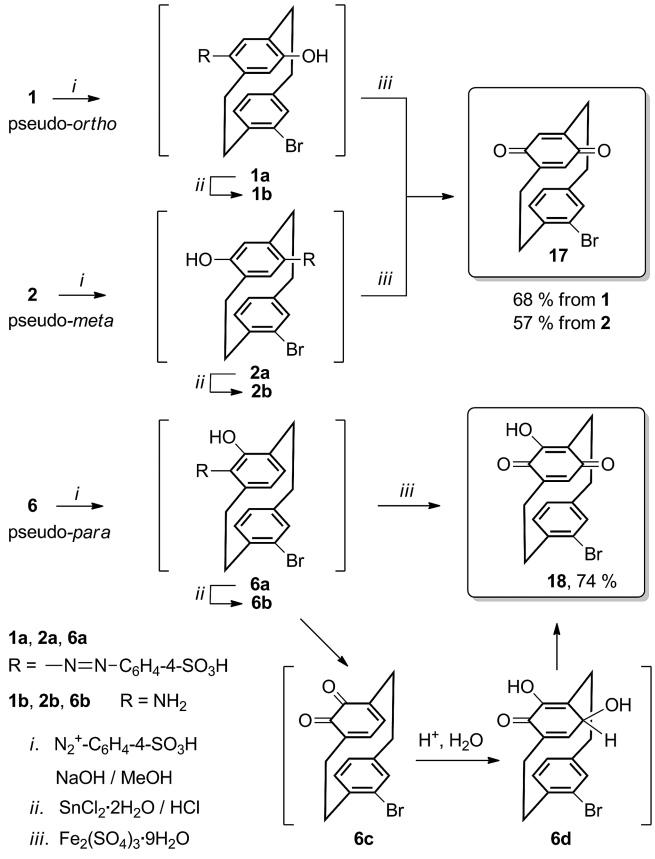


Figure 3. Enantiomerically pure [2.2]paracyclophane-4,7-quinone (**14**) and compounds **15** and **16** obtained therefrom.

Previously, substituted [2.2]paracyclophane-derived quinones were prepared by multistep procedures involving the synthesis of dithia[3.3]paracyclophanes from the respective suitably substituted molecular halves followed by photoextrusion of sulfur.[17] For the synthesis of unsubstituted quinone **14**, either racemic[7e,18] or in enantiomerically pure form,[15,16] an efficient one-pot diazonium coupling/reduction/oxidation sequence starting from **11** was used. As the next step, we evaluated the possibility of the synthesis of substituted planar chiral quinones by applying this sequence of reactions to regioisomeric bromophenols **1**, **2**, and **6** (Scheme 3).



Scheme 3. Synthesis of bromo-substituted [2.2]paracyclophane quinones.

In analogy with the behavior of unsubstituted phenol **11**,[7e] the reaction was expected to occur by the *para*-selective coupling of diazonium and phenol followed by reduction of an intermediate azo derivative to an unstable aminophenol and its further oxidation with formation of the *para*-quinoid fragment. Thus, *para*-diazonium coupling in pseudo-*ortho*-bromophenol (**1**) and in pseudo-*meta*-bromophenol (**2**) would produce azo compounds **1a** and **2a**, respectively, which after reduction would give intermediate amines **1b** and **2b** (Scheme 3). Notably, both of them should furnish the same product as a result of oxidation, namely, 12-bromo[2.2]paracyclophane-4,7-quinone (**17**). Indeed, phenols **1** and **2** showed the predicted reactivity and produced **17** in yields of 68 and 57%, respectively. These reactions are complementary to each other in the synthesis of **17**. Thus, the total three-step synthesis of racemic **17** from [2.2]paracyclophane is more efficient because pseudo-*meta* dibromide could be obtained in good yield by direct bromination of the parent hydrocarbon,[10] and further, the synthesis of **2** did not require low temperatures. In turn, for the synthesis of nonracemic **17**, enantiomers of **1** are the starting materials of choice. pseudo-*para*-Bromophenol (**7**) did not react as predicted and gave rise to 15-bromo-5-hydroxy-[2.2]paracyclophane-4,7-quinone (**18**) bearing a hydroxy

group in addition to the *para*-quinoid fragment. The structures of substituted quinones **17** and **18** were unequivocally established by X-ray diffraction analysis (Figure 4).

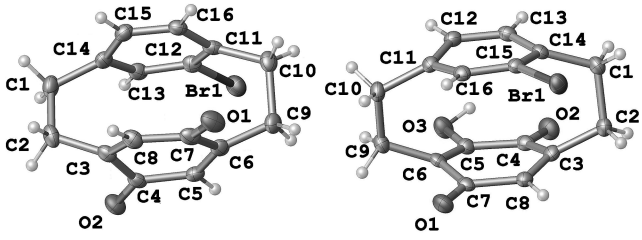


Figure 4. Molecular view of 12-bromo-4,7-dihydro[2.2]paracyclophane-4,7-quinone (**17**, left) and 15-bromo-5-hydroxy-4,7-dihydro-[2.2]paracyclophane-4,7-quinone (**18**, right); thermal ellipsoids given with $p = 50\%$.

To rationalize the formation of **18** one can assume that diazonium coupling in **6** occurs at the *ortho* position rather than the *para* position with respect to the hydroxy group with formation of intermediate azo derivative **6a** owing to steric hindrance exerted by the bromine atom. The reduction of **6a** should produce *ortho*-aminophenol **6b**, which in turn should be transformed into *ortho*-quinone **6c** under oxidation conditions, as is known for the oxidation of aromatic *ortho*-aminophenols.[19] However, *ortho*-quinones formed as intermediates during oxidation of sterically hindered diphenols (such as 3,6-di-*tert*-butylcatechol) in aqueous protic media or under the influence of Fe^{III} salts could suffer hydroxylation followed by several transformations to yield hydroxy-substituted *para*-quinones.[20] These reactions occur by ionic and/or radical mechanisms, respectively. In our case, whereas all successive transformations from **6** to **18** are performed as a one-pot reaction, intermediate *ortho*-quinone **6c** could be hydroxylated by H_2O and the hydroxy group would add to the position that is not shielded by the bromine atom. Subsequent oxidation of **6d** under the action of the Fe^{III} salt that is present in the reaction mixture in excess amounts would lead to hydroxylated *para*-quinone **18**.

The synthesis of the novel bromo-substituted phenols was performed on a gram scale. All transformations were performed with racemic compounds with the aim to study the reactivity of the substrates in the reactions under investigation. There is no doubt that all of the compounds could be obtained in enantiomerically pure form (if needed for certain applications) starting from nonracemic precursors (e.g., **2**, **11**) or by resolution and other chiral transformations fairly well developed for both bromine[21] and the hydroxy group.[22] Stepwise application of classical synthetic techniques, for example, bromine–lithium exchange reactions, and novel approaches, such cross-coupling reactions (Suzuki, Sonogashira, etc.),[23] as well as transformations of the quinoid fragment opens up broad prospects for the synthesis of novel polysubstituted compounds with desired structures and properties. Thus, *ortho*, pseudo-*ortho*, and pseudo-*gem* substitution of [2.2]paracyclophane plays an important role in the construction of chiral promoters,[1,3a] whereas derivatives of *para* and pseudo-*para* substitution patterns are of great interest for applications in polymer and materials chemistry.[2,3b,24]

Conclusions

We elaborated efficient procedures for the gram-scale synthesis of several novel monobromo- and dibromo-substituted 4-hydroxy[2.2]paracyclophanes with various substitution patterns, including a quite rare example with two bromine atoms positioned *meta* to each other. The application of the one-pot diazonium coupling/reduction/oxidation sequence to monobromo-substituted phenols allowed us to obtain substituted [2.2]paracyclophane-4,7-quinones. The newly synthesized planar chiral building blocks combine bromine atoms, hydroxy group, and/or a quinoid fragment in their structures, and they are ready for a number of other transformations (including resolution into enantiomers).

Experimental Section

Bromination of 4-Hydroxy[2.2]paracyclophane (11): A solution of Br_2 (0.50 mL, 1.6 g, 10 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a solution of **11** (2.24 g, 10 mmol) in dichloromethane (50 mL), and the mixture was stirred at room temperature for 4 h. The solution was washed with H_2O (20 mL) and saturated aqueous $NaHCO_3$ solution (2× 30 mL). The aqueous layer was extracted with CH_2Cl_2 (3× 15 mL), and the combined organic solution was dried with Na_2SO_4 and concentrated in vacuo to yield a mixture of compounds **4** and **5**, which were separated by column chromatography (CH_2Cl_2/hexane, 3:2).

Dibromination of Phenol 11: A solution of Br_2 (0.55 mL, 1.76 g, 11 mmol) in CH_2Cl_2 (5 mL) was added to a solution of **11** (1.12 g, 5 mmol) in dichloromethane (30 mL), and the mixture was stirred at room temperature for 4 h. The solution was washed with H_2O (20 mL) and saturated aqueous $NaHCO_3$ solution (2× 30 mL). The aqueous layer was extracted with CH_2Cl_2 (3× 15 mL), and the combined organic solution was dried with Na_2SO_4 and concentrated in vacuo to produce a mixture of **12** and **13**, which were separated by column chromatography (benzene/hexane, 7:3).

General Synthesis of Substituted [2.2]Paracyclophane-4,7-quinones from Phenols 1, 2, and 6: Sodium nitrite (0.245 g, 3.55 mmol) was added to a solution of sulfanilic acid (0.56 g, 3.24 mmol) and Na_2CO_3 (0.171 g, 1.62 mmol) in H_2O (15 mL) cooled to +15 °C. The mixture was stirred for 30 min and poured into a mixture of ice (15 g) and concentrated HCl (0.36 mL, 4.26 mmol). A yellow solution of the diazonium salt was stirred at 0 °C for 30 min. A solution of the respective 12/15/16-bromo-4-hydroxy[2.2]paracyclophane **1**, **2**, or **6** (0.65 g, 2.15 mmol) in MeOH (75 mL) was mixed with a solution of NaOH (0.47 g, 11.81 mmol) in H_2O (10 mL), and the mixture was cooled to 5 °C. Then, a solution of the diazonium salt was added under vigorous stirring, and the temperature was maintained at no higher than +5 °C. The dark-scarlet solution of the azo compound was stirred at +5 °C for 1 h, warmed to room temperature, and left overnight. Concentrated HCl (10 mL) and a solution of $SnCl_2 \cdot 2H_2O$ (3.35 g, 14.85 mmol) in concentrated HCl (13 mL) were successively added to the solution of the azo compound, and the mixture was heated at reflux for 1 h. $Fe_2(SO_4)_3 \cdot 9H_2O$ (29.51 g, 52.5 mmol) was added, and the mixture was heated at reflux with stirring for 8 h. The bromoquinones were

extracted with $CHCl_3$ and dried with Na_2SO_4. The solution was concentrated in vacuo, and the residue was purified by column chromatography ($CHCl_3$).

12-Bromo[2.2]paracyclophane-4,7-quinone (17): Yield 0.46 g (68%), from pseudo-*ortho*-bromophenol (**1**), yield 0.39 g (57%) from pseudo-*meta*-bromophenol (**2**). R_f = 0.71 (CH_2Cl_2). Analytically pure **17** was obtained by crystallization from a mixture of toluene/hexane as yellow crystals, m.p. 197.5–198.5 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.24–2.39 (m, 1 H, -CH_2-CH_2-), 2.56–2.69 (m, 1 H, -CH_2-CH_2-), 2.90–3.19 (m, 4 H, -CH_2-CH_2-), 3.20–3.31 (m, 1 H, -CH_2-CH_2-), 3.31–3.42 (m, 1 H, -CH_2-CH_2-), 5.90 (s, 1 H, 5-H), 6.42 (s, 1 H, 8-H), 6.73 (dd, ^3J = 7.8 Hz, ^4J = 1.8 Hz, 1 H, 12-H), 6.88 (d, ^3J = 7.8 Hz, 1 H, 13-H), 6.93 ppm (d, ^4J = 1.8 Hz, 1 H, 16-H). ^{13}C NMR ($CDCl_3$): δ = 26.93, 29.16, 32.89, 33.81, 127.87, 132.11, 132.41, 133.18, 135.26, 135.51, 138.83, 140.93, 149.66, 150.04, 186.50, 187.40 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1654, 1667 (C=O) cm^{-1}. MS (70 eV): *m*/*z* (%) = 318 (23) $[M]^+$, 317 (6) $[M]^+$, 316 (28) $[M]^+$, 300 (7), 298 (8), 290 (16) $[M - CO]^+$, 289 (5) $[M - CO]^+$, 288 (19) $[M - CO]^+$, 275 (12), 273 (21), 259 (7), 257 (7), 238 (14) $[M - Br]^+$, 237 (100) $[M - Br - H]^+$, 222 (50), 221 (19), 220 (10), 219 (33), 209 (52), 208 (18), 207 (9), 195 (17), 194 (29), 192 (14), 191 (38), 190 (9), 189 (6), 184 (8), 181 (27), 180 (9), 179 (6), 178 (6), 169 (10), 167 (15), 166 (43), 165 (44), 153 (8), 152 (9), 141 (16), 140 (6), 139 (6), 115 (21), 103 (21), 102 (6). $C_{16}H_{13}BrO_2$ (317.18): calcd. C 60.59, H 4.13, Br 25.19; found C 60.67, H 4.13, Br 25.02.

15-Bromo-5-hydroxy[2.2]paracyclophane-4,7-quinone (18): Yield 0.53 g (74%). R_f = 0.07 (CH_2Cl_2). Analytically pure **18** was obtained by crystallization from toluene as dark-red crystals, m.p. 192.5–193.5 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.61–2.68 (m, 1 H, -CH_2-CH_2-), 2.70–2.77 (m, 1 H, -CH_2-CH_2-), 2.83–2.90 (m, 2 H, -CH_2-CH_2-), 2.90–2.97 (m, 1 H, -CH_2-CH_2-), 2.99–3.10 (m, 2 H, -CH_2-CH_2-), 3.34–3.41 (m, 1 H, -CH_2-CH_2-), 6.39 (br. s, 1 H, OH), 6.61 (d, ^3J = 7.8 Hz, 1 H, 13-H), 6.66 (s, 1 H, 8-H), 6.86 (dd, ^3J = 7.8 Hz, ^4J = 1.8 Hz, 1 H, 12-H), 6.91 ppm (d, ^4J = 1.8 Hz, 1 H, 16-H). ^{13}C NMR ($CDCl_3$): δ = 21.82, 26.22, 32.46, 33.36, 122.59, 126.76, 129.43, 132.85, 134.81, 134.82, 137.82, 142.71, 145.25, 150.93, 183.35, 186.53 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 1644, 1660 (C=O), 3421 (OH) cm^{-1}. MS (70 eV): *m*/*z* (%) = 334 (21) $[M]^+$, 333 (5) $[M]^+$, 332 (25) $[M]^+$, 317 (6) $[M - OH]^+$, 306 (7) $[M - CO]^+$, 305 (5), 304 (6), 303 (6), 254 (18) $[M - Br]^+$, 253 (100) $[M - Br - H]^+$, 235 (8), 225 (26), 209 (5), 208 (6), 207 (14) (170), 197, 184 (24), 183 (6), 182 (28), 181 (9), 180 (5), 179 (29), 178 (12), 169 (17), 154 (5), 153 (6), 152 (6), 141 (10), 115 (11), 104 (6), 103 (22). $C_{16}H_{13}BrO_3$ (333.18): calcd. C 57.68, H 3.93, Br 23.98; found C 58.05, H 4.25, Br 23.53.

Supporting Information (see footnote on the first page of this article): Experimental details, analytical data for key compounds, ^{1}H NMR and ^{13}C NMR spectra, and crystallographic data.

Acknowledgments

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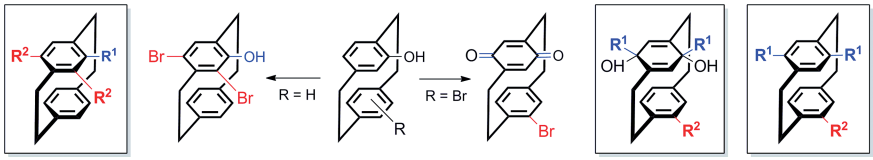

The syntheses of a number of mono- and disubstituted 4-hydroxy[2.2]paracyclophanes and substituted [2.2]paracyclophane-4,7-quinones with various substitution patterns are elaborated. The planar chiral building blocks combine bromine atoms, hydroxy groups, and/or quinoid fragments in their structures, and they are ready for further transformations (including resolution into enantiomers).

Keywords: Cyclophanes / Regioselectivity / Bromination / Chirality / Building blocks / Quinones

