Synthesis of Chiral (*R*)-4-Hydroxy- and (*R*)-4-Halogeno[2.2]paracyclophanes and Group Polarizability. Optical Rotation Relationship

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(*R*)-4-Hydroxy-, -4-fluoro-, -4-bromo-, and -4-iodo[2.2]paracyclophanes have been prepared and their absolute configuration assigned on the basis of chemical correlations. Different relationships between the specific optical rotation and the group polarizability have been found depending on the ability of the substituents to conjugate with the aromatic ring. At least for 4,7-disubstituted [2.2]paracyclophanes, the effects of the substituents on the specific rotation seem to be additive, independent of the wavelength used. An equation has been derived which allows to predict, to a satisfactory approximation, the [α] values of 4-X-7-methyl[2.2]paracyclophanes whenever the group polarizability of the substituents is known.

[2.2]Paracyclophanes constitute an intriguing class of compounds which have attracted the interest of many researchers since their appearance in the literature around the middle of this century.[1] Most studies concern mainly the structural characteristics of [2.2]paracyclophane, [PC], particularly its geometry and its steric, transannular, and ring strains as well as the electronic interations between the aromatic rings having a sandwich form, their influence on reactivity in electrophilic aromatic substitution reactions, and their implications for charge-transfer complex formation.[2] Stereochemical aspects of this system exhibiting a planar symmetry have also been intensively investigated, as witnessed by several works on the circular dichroism of substituted [PC]s.[3] In this paper we wish to report on the synthesis of new chiral monosubstituted [PC]s accompanied by a stereochemical consideration of a possible correlation between the absolute configuration of substituted [PC]s and the sign of their specific rotation.

In our ongoing research, addressed to the exploitation of chiral auxiliary groups with planar symmetry in stereoselective syntheses, we have, for the first time, had to prepare (*R*)-4-hydroxy[PC] [(*R*)-**1**]. We started from the known (*R*)-(−)-4-amino[PC] [(*R*)-**2**],[4] in turn obtained from the racemic modification by fractional crystallization of the diastereoisomeric salts of (1*S*)-(+)-camphorsulfonic acid [(1*S*)-CSA] in ethyl acetate (Scheme 1). Racemic 4-amino[PC] [(±)-**2**] is reported to be prepared in a 34% overall yield by nitration of [PC] followed by H_2/Pd-promoted reduction of the resulting 4-nitro[PC].[4] We prepared racemic **2** more conveniently (46% overall yield from [PC]) by the metalation of 4-bromo[PC] [(±)-**3**] with *n*-butyllithium and successive amination of the resulting 4-lithio derivative with methyllithium−methoxyamine.[5] The treatment of the chiral diazonium fluoroborate (*R*)-**4**

Scheme 1

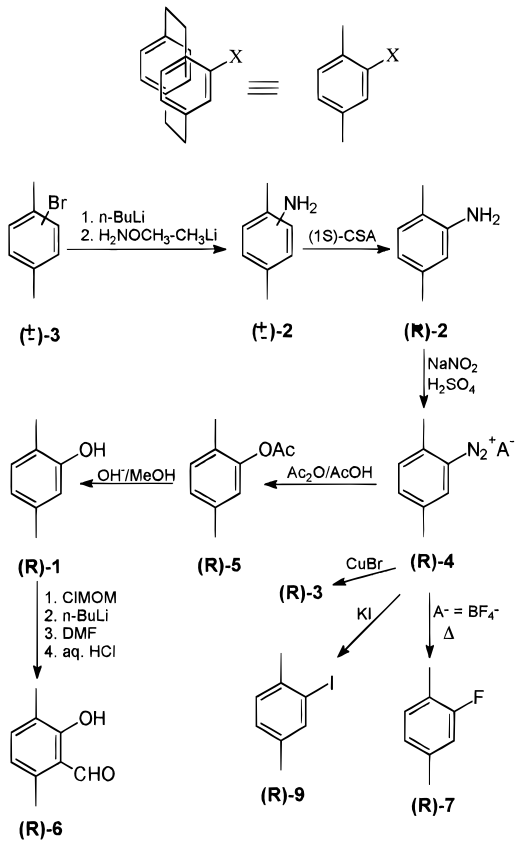

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Table 1. Specific Rotation of Some (*R*)-4-X[2.2]paracyclophanes and the Corresponding Group Polarizability Values of the Substituent

X	$[\alpha]^{20}_D$ (*c*, g/100mL)[a]	group polarizability (P_X)[b]
F	+33.7 (1.11)[c]	0.81
OH	+8.4 (1.22)[c]	1.52
NH_2	−83.5 (0.58)[c]	2.38
CH_3	−75.0[d]	2.59
COOH	−164.0[e]	4.68
CN	−175.0[e]	5.46
$CH{=}CH_2$	−330.0[e]	6.76
Cl	−123.0[e]	5.84
Br	−144.7 (1.02)[c]	8.74
I	−186.6 (0.57)[c]	13.95

[a] Measured in $CHCl_3$ solution. [b] Data from ref 8. [c] From this work. [d] Measured at 25 °C, ref 3d. [e] Data from ref 3c.

with a 1:1 mixture of acetic acid/acetic anhydride at 0 °C gave the corresponding (*R*)-4-acetoxy[PC] [(*R*)-**5**], from which (*R*)-**1** was obtained after alkaline hydrolysis.

Interestingly, whereas all the known (*R*)-4-substituted [PC]s cited in the literature[3] exhibit a negative $[\alpha]^{20}_D$ value, (*R*)-**1** exhibits a positive, although low, specific rotation. In order to remove any doubt about the correctness of our synthetic approach and to confirm the assigned *R* configuration,[6] from (*R*)-**1** we prepared the 5-formyl-4-hydroxy derivative (*R*)-**6**. The latter was previously obtained by resolution of racemic **6** *via* its Schiff's base with (*S*)- and (*R*)-α-phenylethylamine, the absolute configuration being assigned on the basis of crystallographic data.[7] In our synthetic strategy, metalation of MOM-protected (*R*)-**1** with *n*-butyllithium followed by the reaction of the corresponding 5-lithio derivative with *N*,*N*-dimethylformamide gave the MOM-protected 4-hydroxy-5-formyl derivative. After hydrolysis in an acidic medium, a product was obtained which exhibited an $[\alpha]^{20}_D$ value of +587, very similar to that reported in the literature[7] for (*R*)-(+)-5-formyl-4-hydroxy-[2.2]paracyclophane ($[\alpha]^{25}_D = +591$).

At first sight, this finding would show the lack of any connection between the sign of the optical rotation and the absolute configuration. However, doubts could be quickly removed if a certain correlation between the polarizability of the substituent and the $[\alpha]^{20}_D$ value of the corresponding 4-substituted [PC] is considered. The $[\alpha]^{20}_D$ values of (*R*)-4-X[PC]s from this work and from the literature[3] are collected in Table 1 together with the respective group polarizability (P_X).[8]

Interestingly, when the P_X value of each substituent is plotted against the $[\alpha]^{20}_D$ value of the corresponding 4-substituted [PC] (halogeno[PC] being excluded, see below), a satisfactory linear correlation is observed (plot a in Figure 1, $P_X = -0.017[\alpha] + 1.58$, $r = 0.972$). It follows that substituents having P_X values lower than 1.58 are expected to invert the sign of the optical rotation, exactly as is the case of the OH group ($P_{OH} = 1.52$, $[\alpha]^{20}_D = +8.4$). Fluorine has the lowest group polarizability ($P_F = 0.81$); therefore, for (*R*)-4-fluoro[PC] an $[\alpha]^{20}_D$ value more positive than that of (*R*)-**1** would be expected. In order to corroborate this hypothesis we prepared (*R*)-4-fluoro[PC] [(*R*)-**7**] by heating (*R*)-**4** ($A^- = BF_4^-$) gently in xylene. An $[\alpha]^{20}_D$ value of +33.7 was measured for (*R*)-**7** which is in satisfactory agreement with that expected (+45) on the basis of the above correlation.

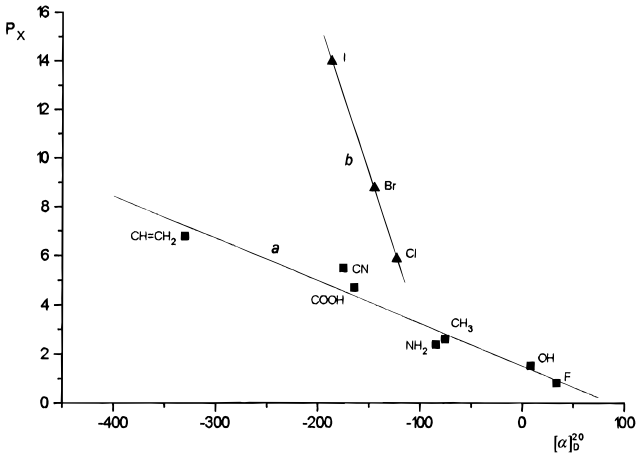

Figure 1. Correlation between the group polarizability (P_X) of the substituent (X) and the specific optical rotation ($[\alpha]^{20}_D$) of (*R*)-4-X[2.2]paracyclophanes.

Turning now our attention to (*R*)-5-chloro[PC] [(*R*)-**8**], the sole enantiomer of the 4-halogeno[PC] series which is reported in the literature,[3c] we may observe a substantial deviation of its $[\alpha]^{20}_D$ value (−123) from that expected on the basis of the above correlation (−250), as though the group polarizability effect of the chlorine on the specific rotation were excessively low compared with those of the above groups. The anomalous behavior of chlorine, in this respect, prompted us to extend our investigation to the remaining (*R*)-4-halogeno[PC]s.[9]

(*R*)-4-Bromo[PC] [(*R*)-**3**] and (*R*)-4-iodo[PC] [(*R*)-**9**] were prepared from (*R*)-**2**, through the corresponding diazonium salt, by the classic Sandmeyer reactions. Both (*R*)-**3** and (*R*)-**9** exhibit negative $[\alpha]^{20}_D$ values abnormally lower than those expected from their group polarizabilities on the basis of the above correlation.

Nevertheless, restricting our analysis to the series I, Br, and Cl, we find a good linear correlation between the group polarizability and the specific rotation. Accordingly, the plot of the P_X values of I, Br, and Cl against the respective specific rotations $[\alpha]^{20}_D$ results in a straight line (plot b in Figure 1, $P_X = -0.127[\alpha] - 9.735$, $r = 0.9998$) having a slope substantially higher than that of plot a. The different behavior of I, Br, and Cl could be explained by assuming that conjugative effects of the substituent with the aromatic ring play a pre-eminent role as compared with that of the group polarizability in affecting the specific optical activity of these chiral aromatic molecules possessing planar symmetry. Accordingly, all the groups considered in plot a have attached to the aromatic ring an atom belonging to the second period of the periodic table so that an extended conjugation involving the outer 2p electrons is made possible. In the halogen series, moving from chlorine to

(6) The enantiomers of 4-hydroxy[PC] have been resolved by enantioselective gas chromatography, but neither the sign of the specific rotation nor the absolute configuration were assigned (König, W. A.; Gehrcke, B.; Hochmuth, D. H.; Mlynek, C.; Hopf, H. *Tetrahedron: Asymmetry* **1994**, *5*, 347).

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(9) The enantiomers of 4-F-, 4-Cl-, and 4-Br[PC] were resolved by chiral HPLC (Hopf, H.; Grahn, W.; Barrett, D. G.; Gerdes, A.; Hilmer, J.; Hucker, J.; Okamoto, Y.; Kaida, Y. *Chem. Ber.* **1990**, *123*, 841), but neither the sign of the specific rotations nor the absolute configurations were reported.

Table 2. Calculated and Experimental [α] Values of (*R*)-4-X- and (*R*)-4-X-7-methyl[2.2]paracyclophanes Determined at Different Wavelengths

	[α]		(*R*)-4-X-7-Me[PC]	
X	(*R*)-4-X[PC]	(*R*)-4-Me[PC]	$[\alpha]_{calcd}$[a]	$[\alpha]_{expt}$
		$[\alpha]^{20-25}_D$ ($CHCl_3$)		
CH_3	−75[b]	−75	−150 (−120)[c]	−155[d]
COOH	−164[e]	−75	−239 (−242)[c]	−224[d]
$COOCH_3$	153[e]	−75	−228	−192[d]
$COCH_3$	−65[e]	−75	−140	−127[d]
		$[\alpha]^{25}_{546}$ ($CHCl_3$)		
CH_3	−114[f,g]	−114	−228	−198 [f,h]
COOH	−198[g]	−114	−312	−284[h]
CH_2OH	−79[h]	−114	−193	−163[h]
CH_2Br	+37[h]	−114	−77	−32[h]

[a] $[\alpha]_{calcd} = [\alpha]_{(R)-4-X[PC]} + [\alpha]_{(R)-4-Me[PC]}$. [b] Reference 3d. [c] Calculated from eq 2 with $m = -0.0172$ and $n = 1.54$ (ref 11). [d] Reference 10a. [e] Reference 3c. [f] In CCl_4. [g] Reference 10c. [h] Reference 10b.

iodine, the conjugation with the aromatic ring is made more and more difficult by the limited overlap of the 3p, 4p, and 5p orbitals (for Cl, Br, and I, respectively) with the 2p orbitals of the phenyl ring. Thus, in this series, atomic polarizability is by far the main effect responsible for the magnitude of the optical rotation.

Finally we wish to report some considerations regarding the individual contribution of the substituents to the specific rotation of polysubstituted [2.2]paracyclophanes. In Table 2, [α] values of some disubstituted (*R*)-4-X-7-methyl[PC]s, available in the literature,[10] are collected together with the [α] values of the corresponding monosubstituted (*R*)-4-X[PC]s measured at the same wavelength. It is of note that the experimental [α] values of disubstituted [PC]s are surprisingly similar to those obtained from the algebraic sum of the [α] values of the two corresponding monosubstituted paracyclophanes, independent of the wavelength employed.

Indeed, the 4 and 7 protons of [2.2]paracyclophane are equivalent, and considering a certain additivity of the effects determining the magnitude and the sign of the specific rotation, the $[\alpha]_{X,Y}$ value of a generic (*R*)-4-X-7-Y[PC] can be assumed to be the sum of the specific rotations $[\alpha]_X$ and $[\alpha]_Y$ of (*R*)-4-X[PC] and (*R*)-4-Y[PC], respectively. If $[\alpha]_X$ and $[\alpha]_Y$ are equally correlated with the group polarizability, as in plot a of Figure 1, we obtain the following equation:

$$P_X + P_Y = m([\alpha]_X + [\alpha]_Y) + 2n \qquad (1)$$

where m is the slope of line a in Figure 1 and n is the P_X value at $[\alpha] = 0$. From eq 1 the $[\alpha]_{X,Y}$ value can be calculated[11] as:

$$[\alpha]_{X,Y} = ([\alpha]_X + [\alpha]_Y) = [(P_X + P_Y) - 2n]/m \qquad (2)$$

The few data available in the literature (Table 2) seem to support this hypothesis, which, however, deserves to be strengthened by relying, of course, upon a higher number of experimental results.

Apart from speculative considerations, we have shown that, as for compounds with central and axial chirality, the optical specific rotation of compounds having a planar chirality is correlated with the group polarizability of the substituents. If the chiral plane is represented by a phenyl ring, the relationship depends on the ability of the outer p orbitals of the substituent to conjugate with the aromatic ring. The above relationship could be a very useful tool to predict not only the sign but also, to a good approximation, the absolute value of the specific rotation of 4-substituted and 4,7-disubstituted [PC]s.

Experimental Section

Reagents were purchased from the Aldrich Chemical Co. and used without further purification. Petroleum ether was the 35−60 °C boiling fraction. Column chromatography was carried out on silica gel 230−400 mesh. ^{1}H-NMR spectra were registered at 200 MHz in a $CDCl_3$ solution using tetramethylsilane as internal reference. All J values are reported in hertz (Hz). Mass spectra were recorded at 70 eV on a GC−MS apparatus. IR spectra were recorded in $CHCl_3$ solutions. If not otherwise specified, optical rotations were measured in $CHCl_3$ solutions on a JASCO-DIP 360 polarimeter at the sodium D line at 20 ± 0.3 °C. For each compound, the maximum difference of the $[\alpha]^{20}_D$ values determined at different concentrations (from 0.5 to 1.5 g/100 mL) was 0.8. The optical purity of (*R*)-**1**, (*R*)-**3**, (*R*)-**7**, and (*R*)-**9** was tested by HPLC analysis on a 25 × 0.46 cm cellulose tris(3,5-dimethylphenylcarbamate) column (Chiracel OD, Diacel) using hexane [for (*R*)-**3**, (*R*)-**7**, and (*R*)-**9**] and 9:1 hexane/2-propanol [for (*R*)-**1**] as the eluent. In no case was *S* enantiomer detected. Satisfactory elemental analyses were obtained for all unknown compounds.

(±)-4-Amino[2.2]paracyclophane, (±)-2. To a stirred solution of methyllithium (0.8 M in diethyl ether, 9.0 mL, 7.0 mmol) was added a solution of methoxyamine (0.33 g, 7.0 mmol) in dry hexane (6 mL) at −78 °C, dropwise under a nitrogen atmosphere.[5] 4-Lithio[2.2]paracyclophane in anhydrous diethyl ether (30 mL), prepared from (±)-**3** (1.0 g, 3.5 mmol) and *n*-BuLi according to the literature,[12] was added all at once, and the mixture was kept at −78 °C for 5 min and then at −15 °C for 2 h. Water was added, and the mixture was extracted with diethyl ether (3 × 25 mL). The collected organic extracts were dried with sodium sulfate, and the solvent was evaporated at reduced pressure. Chromatography of the crude product on silica gel (eluent 8:2 *n*-hexane/diethyl ether) allowed us to isolate pure (±)-**2** (0.4 g, 51%, 46% overall yield from [2.2]paracyclophane): mp 239−241 °C (from ethanol) (lit.[4] mp 239−241.5 °C).

(*R*)-(−)-4-Amino[2.2]paracyclophane, (*R*)-2. To a stirred solution of (±)-**2** (2.5 g, 11 mmol) in ethyl acetate (80 mL) was added (1*S*)-(+)-10-camphorsulfonic acid (2.5 g, 11 mmol), and the mixture was kept at 0 °C for 48 h. After filtration,[13] the resulting solid (1.8 g) was poured into fresh ethyl acetate (35 mL) and stirred for 60 h at room temperature. The last treatment was repeated one more time. The salt was then filtered and treated with 0.1 N sodium hydroxide to give (*R*)-**2** (0.6 g): mp 239−241 °C (from ethanol); $[\alpha]^{20}_D = -83.5$ (c = 0.58) (lit.[3c] mp 237−240 °C, $[\alpha]^{20}_D = -84$); ^{1}H-NMR δ 7.15 (dd, J = 7.8, 1.8, 1 H), 6.6−6.0 (m, 5 H), 5.36 (d, J = 1.4, 1 H), 3.3 (br s, 2 H), 2.55−3.15 (m, 8 H); IR 3485, 3400, 3008−2870, 1620, 1500, 1430, 1103 cm^{-1}; MS m/z (rel intensity) 223 (M^+, 26), 119 (100), 91 (16). Anal. Calcd for $C_{16}H_{17}N$: C, 86.06; H, 7.67; N, 6.27. Found: C, 85.92; H, 7.81; N, 6.38.

(*R*)-4-Diazoniumyl[2.2]paracyclophane Tetrafluoroborate, (*R*)-4 ($A^- = BF_4^-$). (*R*)-**2** (1.2 g, 5.4 mmol) was added to a stirred solution of 96% H_2SO_4 (0.5 mL) in water (65 mL). The mixture was purged with nitrogen and then heated to 85 °C, under nitrogen bubbling, until a clear solution resulted. After 25 min, the solution was cooled at −1 to −3 °C, a saturated aqueous solution of $NaBF_4$ (6.25 g, 56.8 mmol) was added all at once, and then an aqueous solution of $NaNO_2$ (0.62 g, 9.3 mmol in 13 mL of water) was added dropwise. The

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(11) The values of −0.0172 and 1.54 for m and n, respectively, have been calculated including the fluorine data in plot a of Figure 1.

(12) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3534.

(13) The process is favored by adding some crystals of (*R*)-**2**-enriched camphorsulfonic salt to induce the crystallization.

temperature was allowed to rise to 10−15 °C, and stirring was continued for another 30 min. The resulting precipitate was filtered, washed first with cold water, and then with diethyl ether, and finally dried under vacuum to obtain 1.4 g of (*R*)**-4** which was used without purification.

(*R*)-(−)-4-Acetoxy[2.2]paracyclophane, (*R*)-5. (*R*)-4 ($A^- = BF_4^-$) (0.3 g, 0.9 mmol) was added to a mixture of AcOH (1.8 mL) and Ac_2O (2.4 mL) at 0 °C. After a rapid evolution of nitrogen, the mixture was kept for 2 h at room temperature, then diluted with cold water (10 mL), and extracted with $CHCl_3$ (3 × 5 mL). The usual workup and purification of the crude product by chromatography on silica gel (eluent 9:1 petroleum ether/ethyl acetate) gave (*R*)**-5** (0.12 g, 45%): mp 122−123 °C (from hexane) [lit.[14] mp 132.5−134 °C (racemic mixture)]; $[\alpha]^{20}_D = -41.2$ (*c* = 1.02); ^{1}H-NMR δ 6.88 (dd, *J* = 7.8, 1.9, 1 H), 6.50−6.38 (m, 5 H), 5.98 (s, 1 H), 3.2−2.6 (m, 8 H), 2,31 (s, 3 H); IR 3020−2870, 1750, 1603, 1375, 1230, 1022, 914, 721 cm^{-1}; MS *m*/*z* (rel intensity) 266 (M^+, 14), 224 (14), 209 (4), 120 (100), 104 (59), 91 (28), 51 (9), 43 (64). Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.88; H, 6.96.

(*R*)-(+)-4-Hydroxy[2.2]paracyclophane, (*R*)-1. (*R*)-5 (0.30 g, 1.1 mmol) was added to a methanolic solution of KOH (0.5 M, 5 mL) and the mixture stirred for 30 min at room temperature. Water (50 mL) was added; the product was extracted with diethyl ether (3 × 25 mL) and worked up as above to give (*R*)**-1** (0.23 g, 91%): mp 232−234 °C [lit.[14] mp 223−228 °C (racemic mixture)]; $[\alpha]^{20}_D = +8.4$ (*c* = 1.22); ^{1}H-NMR δ 6.98 (dd, *J* = 7.8, 1.9, 1 H), 6.54 (dd, *J* = 7.8, 1.9, 1 H), 6.50−6.35 (m, 3 H), 6.25 (dd, *J* = 7.7, 1.6, 1 H), 5.51 (d, *J* = 1.6, 1 H), 4.49 (br s, 1 H), 3.40, 2.55 (m, 8 H); IR 3604, 3320, 3030, 2943, 1422, 1219, 750 cm^{-1}; MS *m*/*z* (rel intensity) 224 (M^+, 31), 120 (100), 104 (43), 91 (26), 51 (5). Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.74; H, 7.28.

(*R*)-(+)-5-Formyl-4-hydroxy[2.2]paracyclophane, (*R*)-6. To a solution of the sodium salt of (*R*)**-1**, prepared by the reaction of (*R*)**-1** (11.2 g, 50 mmol) with NaH (55 mmol) in a 9:1 mixture (400 mL) of anhydrous diethyl ether/DMF (26 mL), was added chloromethyl methyl ether (5.6 mL, 74 mmol) under nitrogen while stirring. After 30 min water (100 mL) was added; the organic phase was separated and worked up as above. Chromatography of the resulting oil on silica gel (eluent 9:1 petroleum ether/diethyl ether) allowed us to recover crystalline MOM-protected (*R*)**-1** (12.8 g, 95%). The latter (12 g, 45 mmol) was dissolved in diethyl ether (200 mL) containing TMEDA (85 mmol), and *n*-butyllithium (43 mL, 1.6 M in hexane, 69 mmol) was added at 0 °C under nitrogen while stirring. The mixture was allowed to react for 1.5 h at 0 °C, DMF (6.4 mL, 83 mmol) was added, and the reaction was allowed to proceed for 1 h at room temperature; 5% aq HCl (150 mL) was added, the organic phase was separated and washed with water, and the solvent was evaporated. The resulting crude oil was dissolved in a 1:1 THF/2-propanol mixture (100 mL), concd aq HCl (10 mL) was added, and the clear solution was kept at room temperature for 10 h. After neutralization with 5% aq $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the solvent was evaporated at reduced pressure. Chromatography of the crude product on silica gel (eluent 9:1 petroleum ether/diethyl ether) gave pure (*R*)**-6** (5.0 g, 40%): mp 200−203 °C (from hexane−ethanol); $[\alpha]^{20}_D = +587$ (*c* = 0.51 benzene) (lit.[7] mp 201−204 °C; $[\alpha]^{25}_D = +591$); ^{1}H-NMR δ 11.95 (s, 1 H), 9.79 (s, 1 H), 6.92 (dd, *J* = 7.8, 1.8, 1 H), 6.64 (d, *J* = 7.7, 2 H), 6.41 (dd, *J* = 7.9, 1.8, 1 H), 6.30 (m, 2 H), 3.80−2.75 (m, 7 H), 2.60 (ddd, *J* = 13, 10.1, 5.6, 1 H); IR 3027−2943, 1632, 1425, 1108 cm^{-1}; MS *m*/*z* (rel intensity) 252 (M^+, 43), 148 (13), 147 (20), 120 (16), 104 (100), 91 (19), 51 (7). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.72; H, 6.27.

(*R*)-(+)-4-Fluoro[2.2]paracyclophane, (*R*)-7. A solution of (*R*)**-4** ($A^- = BF_4^-$) (0.3 g, 0.9 mmol) in xylene (50 mL) was gently heated to 40−45 °C until nitrogen no longer evolved. After standing at room temperature for 12 h, the solvent was evaporated at reduced pressure and the residue was purified by chromatography on silica gel (9:1 petroleum ether/diethyl ether as the eluent). Recrystallization of the product from ethanol gave (*R*)**-7** (0.11 g, 54%): mp 234−236 °C; [lit.[15] mp 233−234 °C (racemic mixture)] $[\alpha]^{20}_D = +33.7$ (*c* = 1.11); ^{1}H-NMR δ 7.00−6.88 (m, 1 H), 6.55−6.35 (m, 5 H), 5.90 (dd, *J* = 11.2, 1.6, 1 H), 3.5−2.6 (m, 8 H); MS *m*/*z* (rel intensity) 226 (M^+, 13), 122 (19), 104 (100), 78 (14), 51 (6). Anal. Calcd for $C_{16}H_{15}F$: C, 84.92; H, 6.68. Found: C, 85.19; H, 6.76.

(*R*)-(−)-4-Bromo[2.2]paracyclophane, (*R*)-3. (*R*)**-4** ($A^- = BF_4^-$) (0.3 g, 0.9 mmol) was added to a solution of $CuBr\cdot SMe_2$ (0.6 g, 2.9 mmol) in 48% aqueous HBr (4 mL) at 0 °C. After the nitrogen evolution ceased, the mixture was kept for another 30 min at 0 °C and then for 2 h at room temperature. Water (50 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 25 mL). After the usual workup, chromatography on silica gel (petroleum ether as the eluent) gave pure (*R*)**-3** (0.15 g, 58%): mp 157−158 °C from CH_2Cl_2 [lit.[12] mp 136−138 °C (racemic mixture)]; $[\alpha]^{20}_D = -144.7$ (*c* = 1.02); ^{1}H-NMR δ 7.16 (dd, *J* = 7.8, 1.8, 1 H), 6.6−6.4 (m, 6 H), 3.53−2.73 (m, 8 H); MS *m*/*z* (rel intensity) 288 (15), 126 (15), 184 (10), 182 (10), 104 (100), 51 (5). Anal. Calcd for $C_{16}H_{15}Br$: C, 66.91; H, 5.26. Found: C, 67.08; H, 4.97.

(*R*)-(−)-4-Iodo[2.2]paracyclophane, (*R*)-9. (*R*)**-2** (0.2 g, 0.9 mmol) was added to a stirred solution of 96% H_2SO_4 (0.1 mL) in water (12 mL). The mixture was purged with nitrogen and then heated to 85 °C under nitrogen bubbling, while stirring, until a clear solution resulted. After 25 min, the solution was cooled to −1 to −3 °C and an aqueous solution of $NaNO_2$ (0.12 g, 1.7 mmol in 2.5 mL of water) was added dropwise. The temperature was kept between −5 and −3 °C, and stirring was continued for another 30 min. A solution of KI (0.5 g, 3.0 mmol) in H_2O (2 mL) was added between −1 and −3 °C, and the mixture was allowed to react for 30 min at 0 °C and then for 2 h at room temperature. After extraction with $CHCl_3$ (3 × 25 mL), the collected organic phases were washed first with 10% aq $NaHSO_3$ and then with brine. The usual workup gave a crude product which was purified by chromatography on silica gel (petroleum ether as the eluent) to isolate pure (*R*)**-9** (0.16 g, 53%):[16] mp 179−181 °C (from CH_2Cl_2) [lit.[12] mp 146.5−148.5 °C (racemic mixture)]; $[\alpha]^{20}_D = -186.6$ (*c* = 0.57); ^{1}H-NMR δ 7.24 (dd, *J* = 7.8, 1.8, 1 H), 6.82 (d, *J* = 1.7, 1 H), 6.60−6.38 (m, 5 H), 3.45−2.85 (m, 8 H); MS *m*/*z* (rel intensity) 230 ($M^+ - CH_2C_6H_4CH_2$), 104 (100), 77 (18), 51 (6). Anal. Calcd for $C_{16}H_{15}I$: C, 57.50; H, 4.52. Found: C, 57.31; H, 4.66.

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(16) Compound **9** was previously prepared, in only a 15% yield, by metalation of **3** with *n*-butyllithium and successive reaction with I_2.[12]