Enantiomerically Pure (*R*)- and (*S*)-15-Hydroxy[2.2]paracyclophane-4-carbaldehyde (*iso*-FHPC): A Novel Parent Compound for Planar Chiral Ligands

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Keywords: Cyclophanes / Planar chirality / Resolution into enantiomers / Absolute configuration determination / *N*,*O*-ligands

The planar chiral 15-hydroxy[2.2]paracyclophane-4-carbaldehyde (**2**, *iso*-FHPC) was synthesized and resolved via its Schiff bases **8** by using the enantiomers of α-phenylethylamine. The absolute configurations of the enantiomers of **2** were determined by a combined X-ray diffraction and chemical correlation study. Derivatives **9**, the first representatives of cyclophane-derived aminophenols with a *pseudo-gem* arrangement of the functional groups were synthesized. All new chiral compounds can be regarded as prospective ligands for asymmetric synthesis and catalysis.

Introduction

During our long-lasting project directed at the development of planar chiral paracyclophane derivatives and their application to stereoselective synthesis we repeatedly turned to *ortho*-disubstituted [2.2]paracyclophanes and especially to 5-hydroxy[2.2]paracyclophane-4-carbaldehyde (**1**, 5-formyl-4-hydroxy[2.2]paracyclophane, FHPC, Figure 1) and its derivatives. Thus we have developed several efficient regioselective syntheses of FHPC and several related *ortho*-acylhydroxy[2.2]paracyclophanes and have described the resolution of these compounds into their enantiomers;[1] further functionalization allowed us to extend the range and structural diversity of these chiral ligands.[2] A number of *ortho*-disubstituted chiral paracyclophane derivatives (such as Schiff bases, salen type complexes and others) very effectively cause asymmetric induction in different stereoselective processes.[1a,1c,2b,2c,3] In continuation of the FHPC part of the project we decided to synthesize its structural isomer in which the formyl and hydroxy groups are placed vis-a-vis in both aromatic rings of the paracyclophane core. Ligands of the *pseudo*-geminal type look promising because two proximal functional groups could form a system in which the substituents can coordinate with a metal atom in the course of the reaction and/or affect each other sterically as has already been demonstrated by diethylzinc addition to benzaldehyde[4] and the stereoselective synthesis of linalool.[5]

FHPC, 1 **iso-FHPC, 2**

Figure 1. FHPC 1 and its *pseudo*-geminal isomer, *iso*-FHPC **2**

Thus, in this paper we report the efficient synthesis of a novel representative of pseudo-geminally disubstituted planar chiral [2.2]paracyclophane derivatives, namely 15-hydroxy[2.2]paracyclophane-4-carbaldehyde (**2**, *iso*-FHPC, Figure 1), its efficient resolution into enantiomers and several further transformations.

Results and Discussion

The regioselective introduction of substituents into the *pseudo*-gem position relative to certain functional groups in [2.2]paracyclophanes was discovered by Reich and Cram more than 30 years ago.[6] Since the early 1990s these regularities have increasingly been used for the synthesis of chiral [2.2]paracyclophane derivatives. Most of these com-

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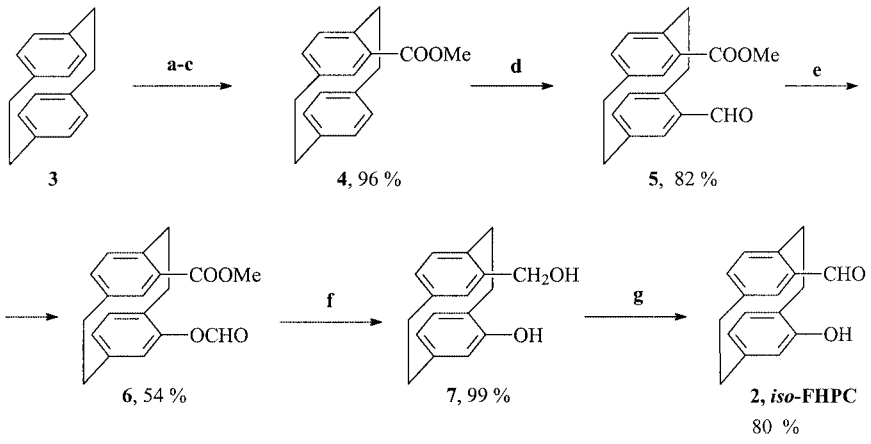
  DOI: 10.1002/ejoc.200200670



a) $(COCl)_2$, $AlCl_3$, -10 °C – -5 °C, 20 min; **b)** PhCl, Δ, 40 h; **c)** MeOH, CH_2Cl_2, Δ, 90 h;
d) $TiCl_4$, Cl_2CHOCH_3, -10 °C – 20 °C, 16 h; **e)** MCPBA, CH_2Cl_2, 20 °C, 16 h;
f) $LiAlH_4$, THF, 60 °C, 6 h, **g)** DDQ, dioxane, 20 °C, 16 h.

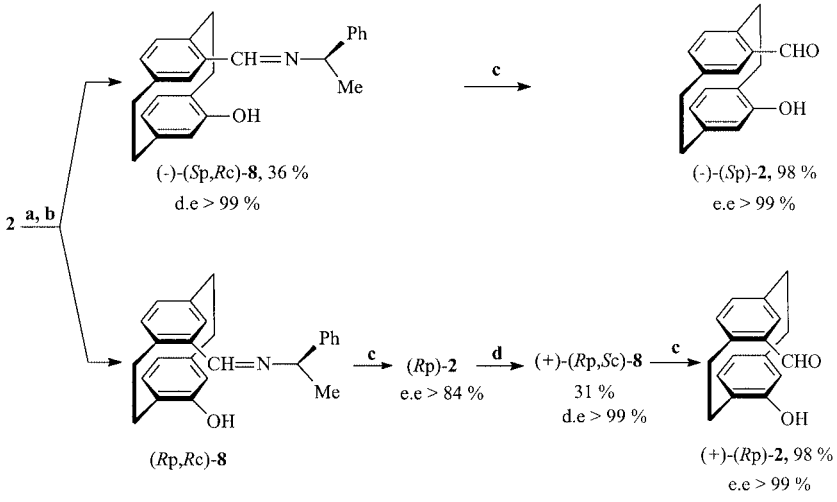
Scheme 1. The preparation of *iso*-FHPC 2 from [2.2]paracyclophane (**3**)

pounds were synthesized by regioselective bromination of 4-carboxy[2.2]paracyclophane derivatives (methyl ester, amides, oxazolines)[4,7] or 4-tosyl[2.2]paracyclophane.[5]

In the present study the method of choice for the generation of the pseudo-geminal substitution pattern was the regioselective $TiCl_4$-catalyzed formylation of 4-methoxycarbonyl[2.2]paracyclophane (**4**) with α,α-dichloromethyl methyl ether recently optimized by us.[8] The complete synthesis of racemic *iso*-FHPC **2**, starting from parent [2.2]paracyclophane (**3**), is outlined in Scheme 1.

The almost quantitative three-step conversion of **3** into the ester **4** was carried out following the literature procedure.[8,9] The formylation of **4** to methyl 15-formyl[2.2]paracyclophane-4-carboxylate (**5**) was presently found to proceed with 2 equivalents of $TiCl_4$ in more concentrated solution and without an inert atmosphere (see Experim. Section), allowing simplification of the whole synthetic procedure without decreasing the chemical yield.

For the introduction of the hydroxy group at the aromatic ring, aldehyde **5** was subjected to a Baeyer–Villiger oxidation. Treating **5** in CH_2Cl_2 at room temperature with commercial *m*-chloroperbenzoic acid (MCPBA) from Aldrich (60%) or Fluka (70%) gave quite poor results, producing methyl 15-formyloxy[2.2]paracyclophane-4-carboxylate (**6**) in yields of 24–37% only. However, preparation of anhydrous MCPBA (87%) from the Fluka reagent increased the yield to 54%. Quantitative reduction of **6** with $LiAlH_4$ provided 15-hydroxymethyl[2.2]paracyclophan-4-ol (**7**),



a) (*R*)-α-PEAM, C_6H_6, mol. sieves 4Å, 80 °C, 6 h; **b)** crystallization from MeOH;
c) 2N HCl, MeOH, Δ, 3 h; **d)** (*S*)-α-PEAM, C_6H_6, mol. sieves 4Å, 80 °C, 6 h.

Scheme 2. Optical resolution of *iso*-FHPC, **2**

which, finally, was effectively oxidized with DDQ in dioxane at room temperature to furnish the target derivative *iso*-FHPC **2** in 80% yield.

For the optical resolution of **2** into its enantiomers an approach, successfully employed earlier for the resolution of FHPC,[1c] was applied: separation of the diastereomeric Schiff bases **8** obtained from **2** with the enantiomers of α-phenylethylamine (α-PEAM, Scheme 2).

Reaction of racemic **2** with (*R*)-α-PEAM resulted in a mixture of (*R*p,*R*c)- and (*S*p,*R*c)-15-{[(1-phenylethyl)-imino]methyl}[2.2]paracyclophan-4-ols **8** in quantitative yield. A single crystallization of the mixture from methanol yielded the levorotatory diastereomer, pure according to ^{1}H NMR and HPLC analysis, in 36% chemical yield. Partially resolved **2** (*ee*, 84%) was recovered from the imine by hydrolysis of the filtrate with aqueous HCl. It was treated with (*S*)-α-PEAM and diastereomerically pure material with positive rotation was isolated in 31% chemical yield (calculated on the starting racemic **2**) after crystallization of the reaction mixture from methanol. X-ray structural analysis[10] revealed the (*R*p,*S*c)-configuration for the dextrorotatory diastereomer of **8** (Figure 2) and hence the (*S*p,*R*c)-configuration was assigned for (−)-**8**.

Individual enantiomers (−)-(*S*p)- and (+)-(*R*p)-**2** were released from the corresponding (−)-(*S*p,*R*c)- and (+)-(*R*p,*S*c)-**8** by almost quantitative hydrolysis with 2 N HCl in methanol. The enantiomeric purity of both enantiomers was additionally checked by HPLC analysis.

As far as the application of **8** as a ligand in stereoselective synthesis is concerned − and taking into account possible differences of the stereochemical influence of the diastereomers in the course of an asymmetric induction − we have deliberately synthesized diastereomerically pure (*S*p,*S*c)-**8** (having negative rotation) from the enantiomerically pure (*S*p)-**2** and (*S*)-α-PEAM (Scheme 3).

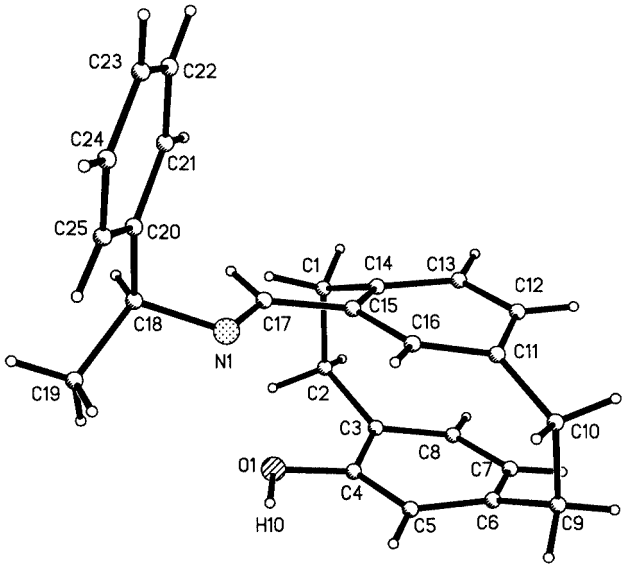
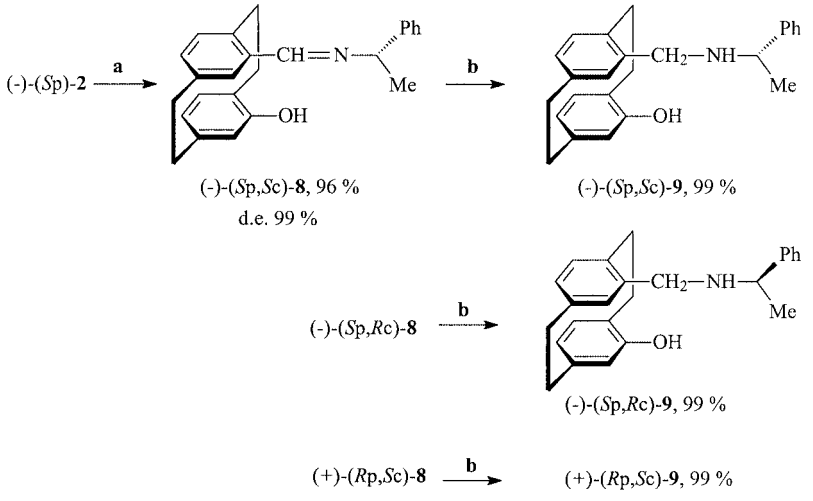


Figure 2. The structure of (+)-(*R*p,*S*c)-**8** in the crystal

As a first example of the extension of the range of planar chiral compounds with *pseudo*-geminal substituent arrangement (derived from *iso*-FHPC) we have prepared the diastereomeric 4-hydroxy-15-[1-phenylethylamino]methyl[2.2]-paracyclophanes **9**. Reduction of the imines (*S*p,*S*c)-, (*S*p,*R*c)-, and (*R*p,*S*c)-**8** with $LiAlH_4$ in anhydrous THF at room temperature gave the corresponding aminophenols (*S*p,*S*c)-, (*S*p,*R*c)-, and (*R*p,*S*c)-**9** in quantitative yield, respectively (Scheme 3). The signs of the optical rotation for all amines were found to be similar to their parent Schiff bases. Moreover in the series of compounds (hydroxyaldehyde **2**, Schiff base **8**, and alkylaminophenol **9**) the sign of the rotation was specified by the chirality of the [2.2]paracy-



a) (*S*)-α-PEAM, C_6H_6, mol. sieves 4Å, 80 °C, 6 h; **b)** $LiAlH_4$, THF, 20 °C, 6 h.

Scheme 3. Preparation of the new *N*,*O*-ligands **9**

clophane moiety, namely (−)- for (*S*p)- and (+)- for (*R*p) derivatives.

In conclusion, we have developed an efficient synthesis of 15-hydroxy[2.2]paracyclophane-4-carbaldehyde (**2**, *iso*-FHPC), resolved it into its enantiomers and demonstrated an easy access to the first representatives of alkylaminophenols with a *pseudo*-geminal arrangement of the functional groups. Obviously, *iso*-FHPC can be regarded as a parent system for a wide family of planar chiral [2.2]paracyclophane ligands (imines, aminophenols, salens, diols etc.) to be used in asymmetric synthesis and catalysis similar to the corresponding derivatives of the well-studied 5-hydroxy-[2.2]paracyclophane-4-carbaldehyde (**1**, FHPC). It should be noted that the range of *pseudo*-geminal disubstituted chiral [2.2]paracyclophane derivatives can also be extended by using the intermediate compounds **5**−**7** as starting materials, which, in turn, could be obtained as enantiomers by application of the transformations presented in Scheme 1 to the enantiomerically pure ester **3**[11] or by possible resolution of the aldehyde **4**.

The application of these new diastereomeric Schiff bases and aminophenols in catalytic diethylzinc addition to aldehydes is in progress.

Experimental Section

General: ^{1}H and ^{13}C NMR spectroscopy: Bruker AMX-400 at 400.13 and 100.61 MHz in $CDCl_3$, C_6D_6, and [D_6]DMSO. For ^{1}H NMR spectroscopy the residual proton signals of the deuterated solvents were used as internal standards (δ_H = 7.27, 7.27, and 2.50 respectively). MS: Kratos MS 90 (70 eV). TLC: silica-gel precoated plates Polygram G/UV$_{254}$ (Machrey-Nagel). Column chromatography: Kieselgel 60 (Merck). HPLC: The enantiomeric purity of *iso*-FHPC **2** was checked on a Chirasel OD-H column, size 0.46 cm i.d. × 25 cm, eluent hexane/isopropanol (9:1), flow 1.0 mL/min, UV detector 254 nm. The diastereomeric purity of the Schiff bases of *iso*-FHPC with α-PEAM **8** was checked on a Chirasel AD-H column, size 0.46 cm i.d. × 25 cm, eluent hexane/isopropanol (9:1), flow 1.0 mL/min, UV detector 254 nm. Optical rotation: EPO-1 in thermostatted cell at 20 °C.

Methyl 15-Formyl[2.2]paracyclophane-4-carboxylate (5): $TiCl_4$ (6.94 mL, 62.7 mol) and Cl_2CHOCH_3 (2.93 mL, 32.6 mmol) were added to a solution of 4-methoxycarbonyl[2.2]paracyclophane (**4**, 8.36 g, 31.4 mmol) in CH_2Cl_2 (250 mL) at −10 °C. The reaction mixture was stirred at −10 °C for 0.5 h, allowed to warm to room temp. and stirred for 20 h at this temperature. The reaction mixture was poured into ice and stirred for 2 h. Aqueous and organic layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic fractions were washed twice with saturated aq. $NaHCO_3$ and NaCl solutions and dried with $MgSO_4$. The solution was passed through a short SiO_2-filled column and the solvent was evaporated. Crystallization from cyclohexane yielded the target compound (6.59 g, 72%). From the filtrate additional **5** (1 g, 10%) was isolated; m.p. 168−169 °C (ref.[8] 169 °C).

Methyl 15-Formyloxy[2.2]paracyclophane-4-carboxylate (6): MCPBA (anhydrous, 87%, 11.74 g, 57.0 mmol) was added in portions to a solution of **5** (11.74 g, 40.0 mmol) in CH_2Cl_2 (240 mL) at room temp. The reaction mixture was stirred overnight, cooled to 0 °C and the precipitated *m*-chlorobenzoic acid was filtered off. The reaction mixture was washed with saturated aq. $NaHCO_3$ and dried with $MgSO_4$. The solvent was evaporated and the residue was purified by SiO_2 chromatography (R_f = 0.68; CH_2Cl_2/Et_2O, 10:1). Recrystallization from Et_2O yielded **6** (6.68 g, 54%); m.p. 156 °C. ^{1}H NMR ($CDCl_3$): δ = 2.77−2.88 ppm (m, 1 H, CH_2-CH*H*), 2.88−3.22 (m, 5 H, C*H*$_2$-C*H*$_2$), 3.22−3.33 (m, 1 H, CH_2-CH*H*), 3.94 (s, 3 H, C*H*$_3$), 4.25−4.34 (m, 1 H, CH_2-CH*H*), 6.14 (d, ^4J = 1.8 Hz, 1 H, 5-H), 6.50−6.75 (m, 2 H, 7-H, 13-H), 6.63 (d, ^3J = 7.8 Hz, 1 H, 8-H), 6.69 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, 12-H), 7.31 (d, ^4J = 1.8 Hz, 1 H, 16-H), 8.13 (s, 1 H, OC*H*O). ^{13}C NMR ($CDCl_3$): δ = 29.9 ppm (C-2), 34.2 (C-1), 34.6 (C-9 or C-10), 34.8 (C-9 or C-10), 51.7 (CH_3), 126.3 (C-5), 128.9, 130.7 (C-7), 130.9, 134.7 (C-16), 135.1 (C-8), 136.2 (C-12), 136.5 (C-13), 139.2, 141.7, 142.6, 148.9, 158.7 (CHO), 167.2 (COO). IR (KBr): $\tilde{\nu}$ = 2987 cm^{-1} (m), 2966 (m), 2946 (m), 2894 (m), 2855 (m), 1730 (vs), 1702 (s), 1451 (m), 1437 (s), 1412 (m), 1295 (m), 1274 (s), 1244 (m), 1223 (s), 1195 (s), 1148 (s), 1133 (s), 1118 (s), 1074 (s), 781 (m), 712 (m). UV (CH_3CN): λ_{max} (log ε) = 286 nm (3.24), 268 (3.54), 224 (4.14), 202 (4.61). MS (EI, 70 eV): *m*/*z* (%) = 310 (85), 282 (48) [M$^+$ − CO], 250 (12), 162 (100), 135 (82), 120 (90), 104 (25). $C_{19}H_{18}O_4$ (310.35), calcd. C 73.53, H 5.85; found C 73.49, H 5.84. Additional crystallization of the filtrate from the same solvent gave 0.815 g of material containing product **6** and starting material **5** in 2:1 ratio (according to ^{1}H NMR analysis).

15-Hydroxymethyl[2.2]paracyclophan-4-ol (7): $LiAlH_4$ (2.9 g, 76.3 mmol) was added to a solution of **6** (5.67 g, 18.3 mmol) in anhydrous THF (550 mL) under argon. The reaction mixture was stirred at 60 °C for 6 h. Unchanged $LiAlH_4$ was destroyed by addition of wet EtOAc and water, and the reaction mixture was acidified with 2 N aqueous HCl until the precipitate had entirely dissolved. The organic phase was separated and the aqueous phase was extracted with EtOAc (2 × 100 mL) and Et_2O (2 × 100 mL). The combined organic layers were washed with water, saturated aq. $NaHCO_3$ solution, water (15 mL), and dried with $MgSO_4$. The solvent was evaporated to yield **7** (4.62 g, 99%); m.p. 210 °C. ^{1}H NMR ([D_6]DMSO): δ = 2.45−2.89 ppm (m, 1 H, 2-H$_A$), 2.67−2.72 (m, 3 H, 9- and 10-H), 2.85−2.89 (m, 1 H, 9- or 10-H), 3.22−3.27 (m, 3 H, 1-H, 2-H$_B$), 4.35−4.39 (m, 1 H, 17-H$_B$), 4.43−4.45 (m, 1 H, -OH), 4.71 (dd, ^2J = 12.3, ^3J = 5.1 Hz, 1 H, 17-H$_A$), 5.54 (d, ^3J = 7.6 Hz, 1 H, 5-H), 5.96 (dd, ^3J = 7.6, ^4J = 1.6 Hz, 1 H, 7-H), 6.20 (d, ^3J = 7.6 Hz, 1 H, 13-H), 6.22 (d, ^3J = 7.6 Hz, 1 H, 8-H), 6.29 (d, ^3J = 7.6 Hz, 1 H, 12-H), 6.36 (d, ^4J = 1.7 Hz, 1 H, 16-H), 8.62 (s, 1 H, -OH). ^{13}C NMR ([D_6]DMSO): δ = 29.4 ppm (C-2), 30.8 (C-1), 34.6 (C-9 or C-10), 34.7 (C-9 or C-10), 61.8 (CH_2), 121.0 (C-5), 123.9 (C-7), 124.8, 131.5 (C-12), 131.8 (C-16), 134.3 (C-13), 134.6 (C-8), 137.4, 137.9, 140.6, 140.8, 155.9. IR (KBr): $\tilde{\nu}$ = 3434 cm^{-1} (br., vs), 3201 (br., vs), 3025 (m), 2976 (m), 2956 (s), 2930 (vs), 2890 (s), 2853 (m), 1598 (m), 1434 (s), 1419 (vs), 1271 (m), 1235 (vs), 1110 (m), 1009 (vs), 998 (vs), 884 (s), 875 (s), 765 (m), 711 (m). UV (CH_3CN): λ_{max} (log ε) = 242 nm (3.76), 228 (4.18). MS (EI, 70 eV): *m*/*z* (%) = 254 (26) [M$^+$], 236 (100) [M$^+$ − H_2O], 134 (24) [$C_8H_7CH_2OH^+$], 120 (100) [$C_8H_7OH^+$], 105 (48), 91 (90), 77 (20). $C_{17}H_{18}O_2$ (254.33), calcd. C 80.28, H 7.13; found C 80.16, H 7.15.

15-Hydroxy[2.2]paracyclophane-4-carbaldehyde (2, *iso*-FHPC): A solution of DDQ (4.12 g, 18.2 mmol) in anhydrous dioxane (120 mL) was added at room temp. to a solution of **7** (4.62 g, 18.2 mmol) in anhydrous dioxane (280 mL). The reaction mixture was stirred at room temp. for 16 h, and the precipitated $DDQH_2$ was filtered off. The solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 and separated from the remaining $DDQH_2$ by

filtration. Silica-gel column chromatography (R_f = 0.30, CH_2Cl_2/Et_2O, 10:1) gave **2** (3.67 g, 80%); m.p. 221 °C. ^1H NMR ([D$_6$]DMSO): δ = 2.55−2.62 ppm (m, 1 H, 2-H$_B$), 2.79−3.10 (m, 5 H, 1-H$_B$, 9-, 10-H), 3.25−3.32 (m, 1 H, 2-H$_A$), 3.93−4.01 (m, 1 H, 1-H$_A$), 5.50 (d, ^4J = 1.8 Hz, 1 H, 5-H), 6.18 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1 H, 7-H), 6.36 (d, ^3J = 7.8 Hz, 1 H, 8-H), 6.54 (d, ^3J = 7.8 Hz, 1 H, 13-H), 6.79 (dd, ^3J = 7.8, ^4J = 1.9 Hz, 1 H, 12-H), 6.97 (d, ^4J = 1.8 Hz, 1 H, 16-H), 8.88 (s, 1 H, -OH), 10.18 (s, 1 H, -CHO). ^{13}C NMR ([D$_6$]DMSO): δ = 29.5 ppm (C-1), 29.6 (C-2), 34.1 and 34.2 (C-9, -10), 121.6 (C-5), 122.9 (C-7), 125.0, 133.0 (C-16), 134.3, 134.7 (C-8), 135.9 (C-13), 136.7 (C-12), 139.2, 140.9, 143.3, 155.7, 190.9 (CHO). IR (KBr): $\tilde{\nu}$ = 3386 cm^{-1} (br., s), 2954 (m), 2929 (s), 2892 (m), 2852(m), 1659 (vs), 1588 (vs), 1578 (vs), 1555 (m), 1418 (vs), 1322 (m), 1272 (s), 1232 (s), 1182 (m), 1160 (m), 1144 (m), 1104 (s), 719 (s), 664 (m). UV (CH_3CN): λ_{max} (log ε) = 284 nm (3.58), 242 (3.93), 238 (3.94), 214 (4.52). MS (EI, 70 eV): *m*/*z* (%) = 252 (80) [M$^+$], 132 (12) [$C_8H_7CHO^+$], 120 (100) [$C_8H_7OH^+$], 91 (18). $C_{17}H_{16}O_2$ (252.31), calcd. C 80.93, H 6.39; found C 80.78, H 6.36.

Resolution of 15-Hydroxy[2.2]paracyclophane-4-carbaldehyde (2): A solution of racemic **2** (1.23 g, 4.88 mmol) and (*R*)-α-PEAM (0.74 g, 0.78 mL, 6.12 mmol) in benzene (40 mL) was refluxed in a flask equipped with a Dean−Stark trap filled with 4-Å molecular sieves for 6 h. The solvent was removed and the resulting mixture of diastereomeric (*S*p,*R*c)- and (*R*p,*R*c)-**8** was recrystallized from methanol to give (*S*p*R*c)-15-{[(1-phenylethyl)imino]methyl}[2.2]-paracyclophan-4-ol (*S*p,*R*c)-**8** (0.622 g, 36%, *de* > 99% by HPLC analysis); m.p. 150−151 °C. $[\alpha]_D^{20}$ = −415 (*c* = 0.27, toluene). ^1H NMR (C_6D_6): δ = 1.67 ppm (d, *J* = 6.5 Hz, 3 H, C*H*$_3$), 2.50−2.89 (m, 6 H, C*H*$_2$-C*H*$_2$), 3.40−3.52 (m, 1 H, CH$_2$-CH*H*), 3.66−3.78 (m, 1 H, CH$_2$-CH*H*), 4.37−4.46 (q, *J* = 6.5 Hz, 1 H, C*H*), 4.80 (br. s, 1 H, O*H*), 5.56 (d, *J* = 1.8 Hz, 1 H, 5-H), 6.18 (dd, J_1 = 7.8, J_2 = 1.8 Hz, 1 H, 7-H), 6.28 (d, *J* = 7.8 Hz, 1 H, 13-H), 6.34 (d, *J* = 7.8 Hz, 1 H, 8-H), 6.41 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, 12-H), 7.20 (t, ^3J = 7.5 Hz, 1 H, *p*-H, Ph), 7.27−7.35 (t, ^3J = 7.5 Hz, 2 H, *m*-H, Ph and 1 H, 16-H), 7.50−7.58 (d, ^3J = 7.5 Hz, 2 H, *o*-H, Ph), 8.54 (s, 1 H, C*H*=N). ^{13}C NMR (C_6D_6): δ = 24.98 ppm (CH$_3$), 30.49 and 32.01 (C-1 and C-2), 34.89 and 35.09 (C-9 and C-10), 70.34 (N-CH), 122.84 (C-5), 125.43 (C-7), 125.85, 127.05 (2 C, *o*-C, Ph), 127.16 (*p*-C, Ph), 128.78 (2 C, *m*-C, Ph), 131.77 (C-16), 134.78 (C-12), 135.12 (C-8), 135.63 (C-13), 139.67, 140.74, 141.68, 145.73, 155.94 (C-4), 160.44 (C=N). MS (EI, 70 eV): *m*/*z* (%) = 356 (15) [M$^+$], 355 (44) [M$^+$], 250 (7), 236 (15), 235 (28) 234 (34), 143 (14), 130 (100), 129 (11), 121 (23), 120 (41), 115 (21), 106 (40), 105 (95), 104 (32), 103 (51). $C_{25}H_{25}NO$ (355.48), calcd. C 84.47, H 7.09, N 3.94; found C 84.61, H 7.10, N 3.89.
Compound (*S*p,*R*c)-**8** was hydrolyzed by refluxing it with aq. HCl in methanol. The organic material was extracted with CH_2Cl_2 (2 × 30 mL), the combined extracts were dried with Na_2SO_4, and after removal of solvent (*S*p)-**2** (0.433 g, 35%) was isolated as pale yellow crystals; m.p. 236−237 °C (decomp.). $[\alpha]_D^{20}$ = −441 (*c* = 0.49, $CHCl_3$). $C_{17}H_{16}O_2$ (252.31), calcd. C 80.93, H 6.39; found C 80.73, H 6.58. The combined methanol filtrates, containing partially enriched (*R*p,*R*c)-**8**, after evaporation and hydrolysis, gave partially resolved (*R*p)-**2** (0.76 g, 62%). This compound and (*S*)-α-PEAM (0.44 g, 0.46 mL, 3.64 mmol) afforded (*R*p,*S*c)-**8** (0.536 g, 31%) after crystallization from MeOH; m.p. 149.5−151 °C. $[\alpha]_D^{20}$ = +405 (*c* = 0.23, toluene). $C_{25}H_{25}NO$ (355.48), calcd. C 84.47, H 7.09, N 3.94; found C 85.13, H 7.24, N 3.95. Hydrolysis of (*R*p,*S*c)-**8** gave (*R*p)-**2** (0.374 g, 31%).

(*S*p,*S*c)-15-{[(1-Phenylethyl)imino]methyl}[2.2]paracyclophan-4-ol [(*S*p,*S*c)-8]: This compound was obtained by the reaction of (*S*p)-**2** (0.245 g, 0.972 mmol) and (*S*)-α-PEAM (0.13 g, 0.136 mL, 1.07 mmol) in benzene (10 mL) in 96% chemical yield (0.333 g). An analytically pure sample (0.158 g, 46%) was obtained by crystallization from heptane; m.p. 146.5−148 °C. $[\alpha]_D^{20}$ = −263 (*c* = 0.21, toluene). ^1H NMR (C_6D_6): δ = 1.62 ppm (d, ^3J = 6.5 Hz, 3 H, C*H*$_3$), 2.45−2.59 (m, 1 H, CH$_2$-CH*H*), 2.61−2.90 (m, 5 H, C*H*$_2$-C*H*$_2$), 3.44−3.59 (m, 1 H, CH$_2$-CH*H*), 3.64−3.79 (m, 1 H, CH$_2$-CH*H*), 4.35−4.49 (q, ^3J = 6.5 Hz, 1 H, C*H*-CH$_3$), 4.40 (br. s, 1 H, O*H*), 5.28 (d, ^4J = 1.8 Hz, 1 H, 5-H), 6.15 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC-arom.), 6.23 (d, ^3J = 7.8 Hz, 1 H, PC-arom.), 6.30 (d, ^3J = 7.8 Hz, 1 H, PC-arom.), 6.42 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC-arom.), 7.14 (t, ^3J = 7.5 Hz, 1 H, *p*-H, Ph), 7.30 (t, ^3J = 7.5 Hz, 2 H *m*-H, Ph), 7.50 (d, ^4J = 1.8 Hz, 1 H, 16-H), 7.60 (d, ^3J = 7.5 Hz, 2 H, *o*-H, Ph), 8.64 (s, 1 H, C*H*=N). ^{13}C NMR (C_6D_6): δ = 24.86 ppm (CH$_3$), 30.57 and 31.34 (C-1 and C-2), 34.83 and 35.06 (C-9 and C-10), 70.68 (N-CH), 122.15 (C-5), 125.09 (C-7), 125.78, 127.12 (2 C, *o*-C, Ph), 127.40 (*p*-C, Ph), 129.00 (2 C, *m*-C, Ph), 131.30 (C-16), 134.98 (C-12), 135.26 (C-8), 135.41 (C-13), 139.23, 140.91, 141.60, 145.96, 155.44 (C-4), 159.19 (C=N). MS (EI, 70 eV): *m*/*z* (%) = 356 (12) [M$^+$], 355 (36) [M$^+$], 250 (6), 236 (11), 235 (22), 234 (27), 143 (10), 130 (100), 129 (11), 121 (19), 120 (39), 115 (15), 106 (37), 105 (95), 104 (36), 103 (46). $C_{25}H_{25}NO$ (355.48), calcd. C 84.47, H 7.09, N 3.94; found C 84.51, H 7.21, N 3.97.

(*S*p,*R*c)-15-{[(1-Phenylethyl)amino]methyl}[2.2]paracyclophan-4-ol [(*S*p,*R*c)-9]: $LiAlH_4$ (0.140 g, 4.12 mmol) was added to a solution of (*S*p,*R*c)-**8** (0.276 g, 0.777 mmol) in anhydrous THF (10 mL) at room temp. The reaction mixture was stirred for 6 h, carefully quenched with H_2O, followed by the addition of excess aqueous KOH solution, and extracted with Et_2O. The combined organic solutions were dried with Na_2SO_4, and the solvent was evaporated to give the crude product (0.274 g, 99%). An analytically pure sample (0.195 g, 70%) was obtained by recrystallization from heptane; m.p. 149.5−150.5 °C. $[\alpha]_D^{20}$ = −55 (*c* = 0.2, toluene). ^1H NMR ($CDCl_3$): δ = 1.65 ppm (d, ^3J = 6.5 Hz, 3 H, C*H*$_3$), 2.60−2.71 (m, 1 H, CH$_2$-CH*H*), 2.79−3.06 (m, 5 H, C*H*$_2$-C*H*$_2$), 3.27 (d, ^2J = 12.5 Hz, 1 H, CH*H*-NH), 3.47−3.68 (m, 2 H, C*H*$_2$-C*H*$_2$), 3.81 (d, ^2J = 12.5 Hz, 1 H, CH*H*-NH), 4.04 (q, ^3J = 6.5 Hz, 1 H, C*H*-CH$_3$), 5.53 (d, ^4J = 1.8 Hz, 1 H, 5-H), 6.29−6.42 (m, 4 H, PC-arom.), 6.54 (d, ^3J = 7.8 Hz, 1 H, PC-arom.), 7.30−7.49 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$): δ = 22.69 ppm (CH$_3$), 29.75, 33.12, 34.66, 34.90 (CH$_2$−CH$_2$), 46.91 (*C*H$_2$-NH), 58.81 (N-CH), 124.54, 125.88 (C-5), 126.39 (2 C, *m*-C, Ph), 127.69 (*p*-C, Ph), 128.99 (2 C, *o*-C, Ph), 129.19 (C-16), 130.77, 132.35, 134.75, 135.06, 135.86, 138.30, 138.57, 140.64, 144.02, 155.74 (C-4). MS (EI, 70 eV): *m*/*z* (%) = 357 (10) [M$^+$], 252 (18), 236 (22), 132 (24), 130 (60), 120 (33), 118 (16), 117 (40), 115 (25), 106 (45), 105 (100), 104 (17), 103 (16). $C_{25}H_{27}NO$ (357.50), calcd. C 83.99, H 7.61, N 3.92; found C 83.82, H 7.80, N 3.91.

(*R*p,*S*c)-15-{[(1-Phenylethyl)amino]methyl}[2.2]paracyclophan-4-ol [(*R*p,*S*c)-9] was obtained by a similar quantitative reduction of (*R*p,*S*c)-**8** (0.250 g, 0.704 mmol). An analytically pure sample (0.165 g, 66%) was obtained by recrystallization from heptane; m.p. 149−150.5 °C. $[\alpha]_D^{20}$ = +47 (*c* = 0.2, toluene). $C_{25}H_{27}NO$ (357.50), calcd. C 83.99, H 7.61, N 3.92; found C 83.85, H 7.57, N 3.93.

(*S*p,*S*c)-15-{[(1-Phenylethyl)amino]methyl}[2.2]paracyclophan-4-ol [(*S*p,*S*c)-9] was obtained by quantitative reduction of (*S*p,*S*c)-**8** (0.171 g, 0.42 mmol). An analytically pure sample (0.104 g, 61%) was obtained by crystallization from heptane; m.p. 177.5−178.5 °C. $[\alpha]_D^{20}$ = −78 (*c* = 0.44, toluene). ^1H NMR ($CDCl_3$): δ = 1.63 ppm (d, ^3J = 6.5 Hz, 3 H, C*H*$_3$), 2.53−2.64 (m, 1 H, CH$_2$-CH*H*), 2.79−3.16 (m, 6 H, C*H*$_2$-C*H*$_2$), 3.25 (d, ^2J = 12.5 Hz, 1 H, CH*H*-

NH), 3.50−3.58 (m, 2 H, C*H*H-CH_2), 3.57 (d, ^2J = 12.5 Hz, 1 H, CH*H*-NH), 4.10 (q, ^3J = 6.5 Hz, 1 H, C*H*), 5.57 (d, ^4J = 1.8 Hz, 1 H, 5-H), 6.77 (d, ^3J = 7.8 Hz, 1 H, PC-arom.), 6.34 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC-arom.), 6.40 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC-arom.), 6.48−6.56 (m, 2 H, PC-arom.), 7.33−7.42 (m, 1 H, *p*-H, Ph), 7.43−7.52 (m, 2 H, *m*-H, Ph), 7.54−7.62 (m, 2 H, *o*-H, Ph). ^{13}C NMR ($CDCl_3$): δ = 23.67 ppm (CH_3), 29.74, 32.68, 34.77, 34.95, 46.68 (*C*H_2-NH), 59.06 (*C*H-CH_3), 124.88, 125.64, 127.17, 127.30, 127.82, 128.81, 129.88, 130.72, 132.47, 134.78, 135.03, 138.68, 138.71, 140.74, 142.42, 155.41. MS (EI, 70 eV): *m*/*z* (%) = 358 (11) [M^+], 357 (37) [M^+], 356 (18) [M^+], 355 (10) [M^+], 253 (16), 252 (61), 238 (25), 237 (20), 236 (50), 235 (20), 221 (24), 208 (16), 207 (15), 193 (26), 133 (30), 132 (67), 131 (71), 130 (88), 129 (26), 128 (14), 121 (32), 120 (84), 119 (26), 118 (49), 117 (90), 116 (29), 115 (73), 107 (21), 106 (86), 105 (100), 104 (44), 103 (45), 102 (16). $C_{25}H_{27}NO$ (357.50), calcd. C 83.99, H 7.61, N 3.92; found C 83.89, H 7.70, N 3.92.

Crystal Structure Determination of (*R*p,*S*c)-8: $C_{25}H_{25}NO$ (M = 355.46), orthorhombic, space group $P2_12_12_1$, at 110 K, a = 11.1843(2), b = 12.862(2), c = 26.320(5) Å, V = 3786.1(1) Å^3, Z = 8, $d_{calcd.}$ = 1.247 g·cm^{-3}, μ = 0.075 mm^{-1}, F(000) = 1520, crystal size 0.25 × 0.30 × 0.45 mm. The single-crystal X-ray diffraction experiment was carried out with a Bruker SMART 1000 CCD area detector (graphite monochromated Mo-K_α radiation, λ = 0.71073 Å, ω-scans with a 0.3° step and 10 s per frame exposure, 2θ < 56°, 110 K). Reflection intensities were integrated using the SAINT software [SMART V5.051 and SAINT V5.00, Area detector control and integration software, 1998, Bruker AXS Inc., Madison, WI, 53719, USA]. A total of 25077 reflections was measured, 9121 (R_{int} = 0.0910) independent reflections were used in further calculations and refinement. The structure was solved by the direct method and refined by full-matrix least-squares against F^2_{hkl} in anisotropic approximation. The hydrogen atom of the hydroxy group was located from the difference Fourier syntheses and refined in isotropic approximation. Other hydrogen atoms were placed in geometrically calculated positions and included in the final refinement using the "riding" model. All calculations were performed on an IBM PC/AT using the SHELXTL software [G. M. Sheldrick, SHELXTL-97, Version 5.10, Bruker AXS Inc., Madison, WI, 53719, USA (Bruker SHELXTL), 1997].

Acknowledgments

Financial support of this work by Russian Science Foundation (03-03-32957 and 03-03-32214) and the Fonds der Chemischen Industrie is gratefully acknowledged. The authors are grateful to Prof. V. Davankov and Dr. M. Il'in (Moscow, Russia) for enantiomeric and diastereomeric analysis.

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[10] CCDC-198178 for (*R*p,*S*c)-**8** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44−1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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Received November 29, 2002

