Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2683–2693

TETRAHEDRON: *ASYMMETRY*

Elaboration of a novel type of planar-chiral methylene bridged biphenols based on [2.2]paracyclophanes

Valeria I. Rozenberg,* Dmitrii Yu. Antonov, Roman P. Zhuravsky, Evgenii V. Vorontsov, Viktor N. Khrustalev, Nikolai S. Ikonnikov and Yuri N. Belokon'*

A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilova 28, 117813 Moscow, Russia

Received 13 April 2000; accepted 26 May 2000

Abstract

A new class of chiral methylene bridged biphenols with planar chirality has been designed and elaborated. The synthetic approach is based on the use of 4-hydroxy-5-hydroxymethyl[2.2]paracyclophane **9** derived from either racemic or enantiomerically pure (*S*)-4-formyl-5-hydroxy[2.2.]paracyclophane (FHPC) by reduction with $LiAlH_4$. The condensation of **9** with chiral racemic 4-hydroxy[2.2]paracyclophane **4** and achiral phenols, such as 2,5-dimethylphenol **10** and 2-isopropyl-5-methylphenol **11**, afforded the target bridged biphenols **6**, **12** and **13**, respectively. The preliminary results on the asymmetric addition of Et_2Zn to benzaldehyde promoted by (*S,S*)-**6** are reported.

1. Introduction

Chiral biphenols are widely used as ligands in modern stereoselective synthesis.[1] The key feature of these chiral compounds is their ability to form chelates with metal ions to create various chiral Lewis acids which are efficient catalysts and reagents for asymmetric synthesis.[1] For example, chiral Lewis acids derived from chiral biphenols are often used to catalyze asymmetric versions of numerous reactions such as Diels–Alder and hetero-Diels–Alder reactions; ene, polymerization, allylation, silylcyanation, and carbonylation reactions; aldol type reactions, asymmetric reduction, enantioselective addition of organometallic reagents, etc.[1] However, up to now, axially chiral 1,1′-binaphthalene **1** has remained virtually the only scaffolding for the construction of optically active biphenols to be used in the above reactions. The ligands employed for this purpose differed only in substituents (R,R′ = Alk, Ar, $SiAlk_3$, $SiAr_3$, etc.) in the *ortho*-positions in relation to the hydroxy groups (Fig. 1).[1]

The use of a chiral complex derived from lithium aluminum hydride and axially chiral [9,9′-biphenanthryl]-10,10′-diol **2** for the asymmetric reductions of ketones has also been reported.[2a]

* Corresponding authors. E-mail: yubel@ineos.ac.ru

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00215-9

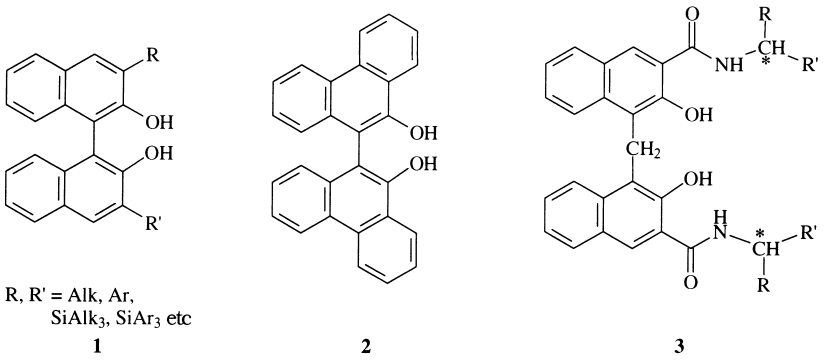


Figure 1.

Bridged biphenol **3**, whose optical activity is due to the asymmetric centers present in the side chain of the molecule, has been synthesized quite recently and tested as a possible HIV-1-protease inhibitor.[2b]

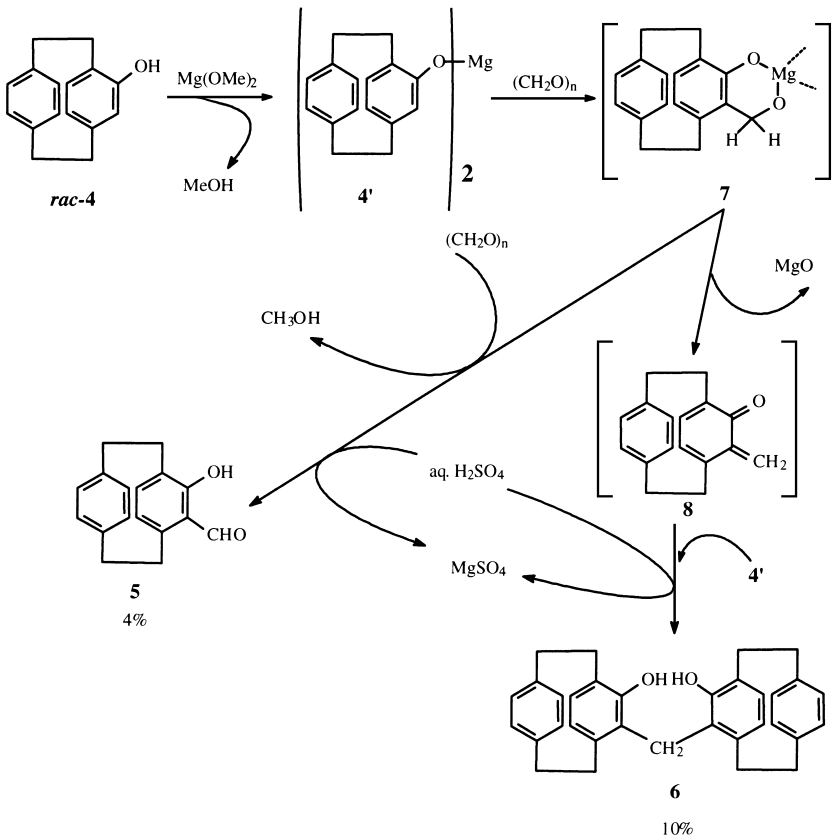
Presently planar-chiral compounds derived from ferrocene[3] and [2.2]paracyclophane are attracting significant attention as efficient reagents and ligands for asymmetric synthesis and catalysis.[4] It would have been of interest to design a new class of planar chiral biphenols, combining advantages of both classes of chiral compounds. Unfortunately, the introduction of a hydroxyl group makes ferrocene highly unstable[5a] and thus unsuitable for the construction of this type of molecules. On the other hand, hydroxy[2.2]paracyclophanes are quite stable compounds[5b,c] and seemed to be appropriate starting materials for the synthesis of this new family of chiral compounds.

In this paper, we describe a general procedure for the preparation of a new type of planar chiral bridged biphenols based on [2.2]paracyclophane in which the hydroxyl-containing aromatic moieties are linked by a methylene bridge located in the *ortho*-position relative to each hydroxyl group. Enantiomerically pure (*S,S*)-bis[5-(4-hydroxy[2.2]paracyclophanyl)]methane (*S,S*)-**6** was synthesized and a preliminary assessment of this compound for use in catalysts for the asymmetric addition of diethylzinc to benzaldehyde was made.

2. Results and discussion

Initially we have chosen the reaction of the magnesium phenoxide derived from 4-hydroxy[2.2]-paracyclophane **4** with formaldehyde as a possible pathway to the target bridged biphenols. Formylation of phenoxides with formaldehyde is well known to give, in addition to salicylaldehydes, 2,2′-dihydroxydiarylmethanes, a side product formed sometimes in substantial amounts.[6] Formylation of magnesium phenoxide **4′** derived from racemic **4** with paraformaldehyde furnished two products, namely, 4-hydroxy-5-formyl[2.2]paracyclophane **5** (FHPC)[7] in a yield of only 4% and the previously unknown bis[5-(4-hydroxy[2.2]paracyclophanyl)]methane **6** in a yield of 10% (Scheme 1). The initial **4** was recovered in a 62% yield.

The formation of **5** can be attributed to the oxidation of the hydroxymethylated derivative **7** by the second equivalent of formaldehyde. The intermediate **7** should also be involved in the formation of bridged products during the reaction· by analogy with the common phenol condensation reactions.[6,8] The competing elimination of magnesium oxide (especially in the absence of donor ligands such as methanol,[6] HMPA, and amines[8]) from compound **7** should give rise to the



Scheme 1.

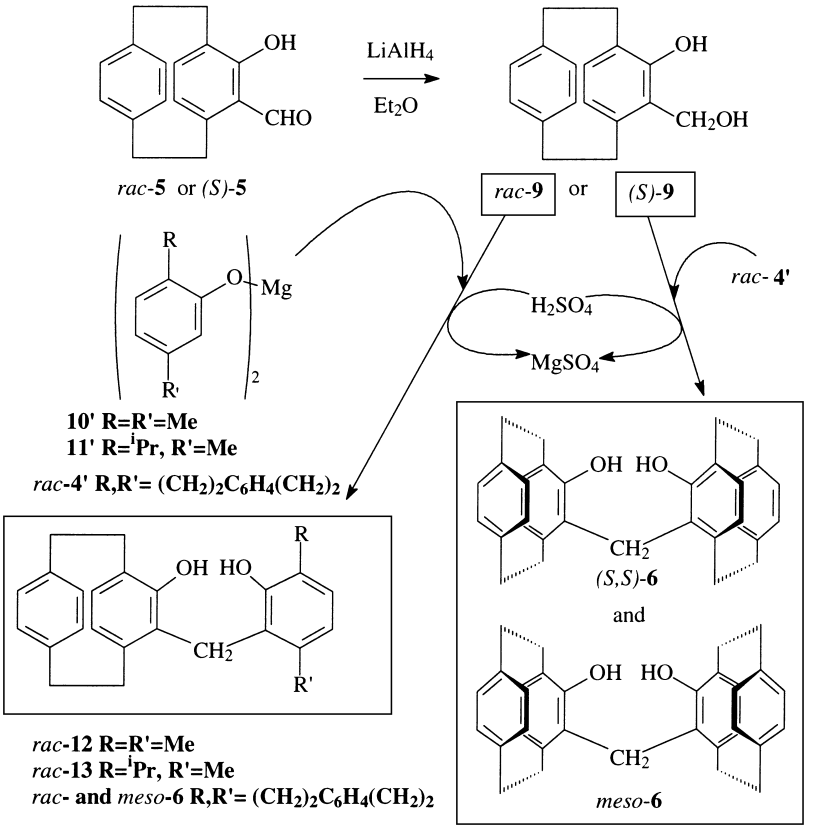
quinone methide intermediate **8**. Most likely, it is this intermediate that alkylates (with exceptional *ortho*-regiospecificity[9]) **4′** to give **6** (see Scheme 1).

The use of racemic phenol **4** should produce bridged biphenol **6** as two diastereomers, namely, the racemic (*R**,*R**)-**6** and *meso*-form (*R*,*S*)-**6**. However, chromatographic separation of the reaction mixture afforded only one diastereomer of **6** in a 10% yield. The signal of the protons of the bridging methylene group in ^{1}H NMR spectra was registered at 3.18 ppm as a sharp singlet. The relative configuration of this compound was established as (*R**,*R**) by synthesis of enantiomerically pure (*S*,*S*)-**6** (vide infra). The *meso*-form was not detected in this experiment.

Although the preparation of chiral bridged biphenol **6** is, in principle, possible by this technique, the approach does not seem to be synthetically useful because the yield of the target bridged biphenol was disappointingly low. In addition only bridged biphenols containing two paracyclophanyl moieties can be prepared via this route. As evidenced by the significant recovery of **4**, it was the low yield of intermediate **7** that was mainly responsible for the poor yield of **6**. Evidently, by using 4-hydroxy-5-hydroxymethyl[2.2]paracyclophane **9** for the alkylation of phenols the competing formation of **5** can be avoided. Also it should become possible to synthesize not only the symmetrical dicyclophanylmethane product **6** but also mixed diarylmethanes. In addition, this approach could open up the way to enantiomerically pure bridged biphenols because optically pure 4-hydroxy-5-hydroxymethyl[2.2]paracyclophane **9** should be readily prepared from enantiomers of **5**.

The use of *ortho*-hydroxy-α-alkylbenzyl alcohols for the alkylation of phenols has already been described previously.[10]

Compound **9** was synthesized in both racemic and enantiomerically pure forms by the reduction of *rac*-**5** and (*S*)-**5** with lithium aluminum hydride in almost quantitative yields. *rac*-**9** was used to alkylate phenol **4**, as well as 2,5-dimethylphenol **10** and 2-isopropyl-5-methylphenol **11** to furnish racemic chiral bridged biphenols **6**, **12** and **13** (Scheme 2). (*S*)-**9** was used to alkylate *rac*-**4** to generate (*S*,*S*)-**6** (Scheme 2). The choice of the phenols was made in such a way that one *ortho*-position in relation to the hydroxyl group should be substituted in order to prevent a side reaction of phenol dialkylation.[6,8]



Scheme 2.

Compound **9** was quite stable as a solid and in acidic solutions. Still, the compound was highly unstable under basic conditions and converted into a polymeric material or/and other unidentified self-condensation materials. To avoid the side reactions of **9**, phenols **4**, **10** and **11** were first converted into the corresponding magnesium phenolates **4′**, **10′** and **11′**, then **9** was added into the reaction mixture and **7** was thus generated in situ by the exchange with the corresponding phenolates. The reaction mixture was kept at 100°C for 2 h, then half of the solvent was evaporated in vacuo, a fresh portion of toluene added, and heating continued for additional 3 h. The reaction mixture was quenched with aq. H_2SO_4 to give finally a target bridged biphenol. Thus the novel bridged biphenols were prepared in yields 64, 76 and 70% for a mixture of (*R**,*R**)-**6** and

meso-**6**, **12** and **13** correspondingly. Notably, compound **6**, as the ^{1}H NMR spectrum of the reaction mixture indicated, consisted of both chiral and *meso*-forms in approximately equal amounts; however, the product isolated by chromatography in 32% yield was (*R**,*R**)-**6**. We were unable to separate *meso*-**6** from the initial phenol **4** (the structure of *meso*-**6** was determined by analyzing the mixture by mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy).

The use of (*S*)-**9**, according to the analysis of the ^{1}H NMR spectra of the reaction mixture, resulted in the ratio of chiral (*S*,*S*)-**6** to *meso*-**6** equal to 1.5:1. The fact that the (*S*,*S*)-form of bridged biphenol **6** predominated meant that one enantiomer of phenol **4** (in this particular case, the (*S*)-enantiomer) reacted faster; hence, the unreacted **4** should have been enriched in the other form (i.e. the (*R*)-form). Unfortunately, the value of the specific rotation angle of **4** ($[\alpha]_D^{25} = 8.4$ for even the enantiomerically pure sample[7]) was low and insufficient to estimate the extent of the enrichment of the remaining partially kinetically resolved **4**. In order to solve the problem, the unreacted phenol **4** was converted into **5** (FHPC), a compound with greater optical rotation angle, [for (*R*)-**5**, $[\alpha]_D^{25}$ +573° (*c* 0.55, benzene)[7]]. For this purpose, the whole mixture of phenol **4** and *meso*-bridged biphenol **6** was subjected to formylation by paraformaldehyde in the presence of $SnCl_4$ and Bu_3N under the same conditions as reported for *ortho*-formylation of **4**.[7] FHPC **5** was readily separable from both **4** and *meso*-**6** (the latter is not formylated under the reaction conditions). As expected, the resulting **5** was enriched in the (*R*)-form, $[\alpha]_D^{25}$ +62 (*c* 0.42, benzene), which corresponded to a 10% enantiomeric excess of (*R*)-**5** and, hence, to a 10% excess of the initial (*R*)-**4**. The observation seems to support the notion of some chiral recognition in the condensation reaction of (*S*)-**9** with racemic **4**.

Bridged biphenol **12** was studied by X-ray diffraction analysis; the bond lengths and bond angles were found to correspond to the mean statistical values. The molecule contains a relatively strong intramolecular hydrogen bond, O(1)···H(2O)-O(2) [O···O 2.733(6) Å, O···H 1.95(5) Å, the O···H-O angle is 147(4)°] (Fig. 2).

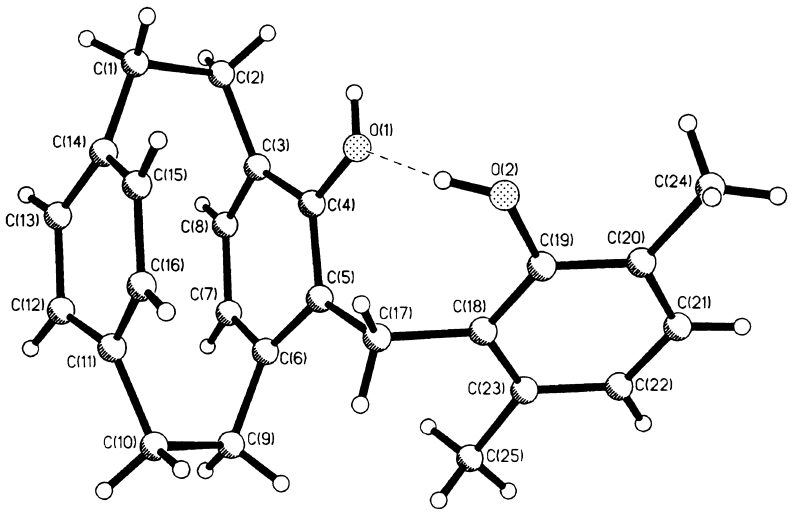
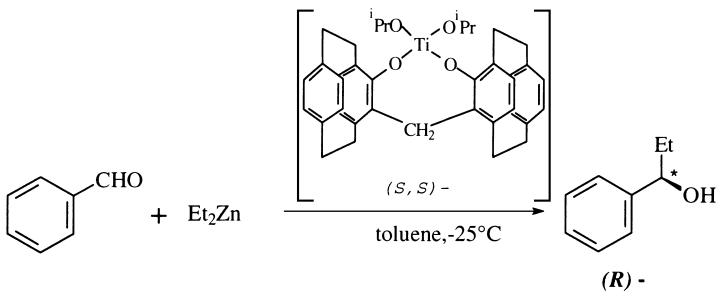


Figure 2. The molecule structure of the [5-(4-hydroxy[2.2]paracyclophanyl)-2-(3,6-dimethyl)hydroxyphenyl)]methane **12**

The enantiomerically pure (*S*,*S*)-**6** prepared in this study was used as a chiral ligand in the asymmetric addition of diethylzinc to benzaldehyde (Scheme 3), employing the approach elaborated earlier by Seebach[11] for TADDOL mediated reactions. The Ti(IV) complex was prepared

by mixing (*S*,*S*)-**6** with 1.2 equivalents of $Ti(O^iPr)_4$ in toluene at room temperature. The solvent, formed isopropanol, and the excess of $Ti(O^iPr)_4$ were removed in vacuo and the remaining complex was used without further purification.



Scheme 3.

As data collected in Table 1 indicated, (*S*,*S*)-**6** did function as an asymmetric inductor in this reaction. Although the observed e.e.'s were relatively small, we hope that this particular type of ligands would perform better in other asymmetric reactions best fit for this particular type of ligands.

Table 1
Enantioselective addition of diethylzinc to benzaldehyde catalyzed by di(isopropyloxy)titanate of (*S*,*S*)-**6**[a]

Entry	Cat. (eq)	Additional amount of $Ti(O^iPr)_4$ (eq)	Conversion, %[b]	e.e. (%)[c]	Config.[d]
1	0.15	1.2	100	22	*R*
2	0.25	0	37	36	*R*

(a) 1.8 eq. of diethylzinc was used, the catalyst (cat.) was prepared *in situ* by mixing *(S,S)*-**6** and $Ti(O^iPr)_4$. (b) Determined by ^1H NMR. (c) Determined by GLC. (d) Determined by GLC using comparison with authentic samples.

3. Conclusion

A new class of planar chiral methylene bridged biphenols based on [2.2]paracyclophane was elaborated and further testing of the compounds in different reactions is under way.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AMX-400 instrument [400.13 (^1H) and 100.61 (^{13}C) MHz] using the residual proton signals of deuterated solvents [$CHCl_3$ ($\delta = 7.27$ ppm) and THF ($\delta = 1.8$ ppm for high-field signal)] as internal standard. EI mass spectra were recorded on a

KRATOS MS890A mass spectrometer (70 eV). Optical rotations were measured using a Perkin–Elmer-241 polarimeter in a temperature-controlled cell at 25°C. TLC analyses were performed on silica precoated plates 'Silufol UV-254' (Chemapol). Column chromatography was carried out on Kieselgel 60 (Merck). A 2 M solution of Et_2Zn was obtained by dilution of Et_2Zn (Aldrich) with toluene. $Ti(O^iPr)_4$ and benzaldehyde were freshly distilled before use. Methanol was distilled from its magnesium alkoxide under argon and stored over 3 Å molecular sieves. Toluene, Et_2O and THF were distilled before use from potassium and sodium benzophenone ketyl, respectively, under argon. Petroleum ether was washed successively with concd H_2SO_4, water and saturated aqueous Na_2CO_3, dried over KOH and distilled over sodium metal.

4.2. GLC enantiomeric analyses of 1-phenyl-1-propanol

The enantiomeric purity of 1-phenyl-1-propanol was checked by GLC for its trifluoroacetyl ester on a DP-TFA-γ-CD phase using a fused silica capillary column (22 m×0.23 mm), 70°C, and He as the carrier gas (1.5 bar).

4.3. X-Ray diffraction study

Crystals of **12** ($C_{25}H_{26}O_2$, $M=358.46$) were orthorhombic, space group $P2_12_12_1$. At 20°C: $a=7.751(4)$, $b=11.477(5)$, $c=20.79(1)$ Å, $V=1849(2)$ Å^3, $Z=4$, $d_{calcd}=1.287$ g/cm^3.

The unit cell parameters and reflection intensities were measured on a Siemens P3/PC four-circle automated diffractometer (λ-MoKα radiation, graphite monochromator, $\theta/2\theta$ scan, $\theta_{max}=25°$). The structure was solved by the direct method and refined by the full-matrix least-squares technique in the anisotropic approximation for nonhydrogen atoms. Hydrogen atoms (except for those of the hydroxy groups, localized objectively in the Fourier difference map and refined isotropically) in the geometrically calculated positions were refined in the isotropic approximation with fixed positional (riding model) and thermal parameters (for hydrogen atoms of CH_3-groups $U_{iso}=1.5U_{iso}$ of parent carbon atoms and for rest hydrogen atoms $U_{iso}=1.2U_{iso}$ of parent carbon atoms). The final discrepancy factors were $R_1=0.065$ for 1288 reflections with $I>2\sigma(I)$ and $wR_2=0.184$ for 1849 independent reflections. All calculations were carried out on an IBM PC/AT-486 computer using the SHELXTL PLUS program package (PC Version 5.0).[12] Full atomic coordinates, bond lengths and angles, and anisotropic temperature factor have been deposited with the Cambridge Crystallographic Data Center: deposition number CCDC-142891.

4.4. Racemic (R*,R*)-bis[5-(4-hydroxy[2.2]paracyclophanyl)]methane (R*,R*)-6. ortho-Formylation of 4-hydroxy[2.2]paracyclophane 4 with paraformaldehyde

Magnesium turnings (0.410 g, 16.9 mmol) and methanol (20 ml) were heated under Ar until the magnesium dissolved and the evolution of hydrogen ceased (1.5 h). 4-Hydroxy[2.2]paracyclophane **4** (6 g, 26.8 mmol) and methanol (10 ml) were added to the solution. The reaction mixture was refluxed for 1 h. Approximately half of the methanol was distilled off and a fresh portion of toluene (25 ml) was added to the residue. The azeotropic mixture of toluene and methanol was removed by fractional distillation, until the temperature of the reaction mixture reached 95°C. A paraformaldehyde powder (8.67 g, 289 mmol) was added to the reaction mixture in small portions over 1.5 h at 95°C. The mixture was stirred for 1 h at 95°C and cooled to 30°C, then 50 ml of 10% aq. H_2SO_4 were added. The resulting mixture was stirred for 2 h at 30–40°C, the aqueous

layer separated and extracted with ether (2×30 ml). The organic layer and the extracts were combined and washed with 10% aq. H_2SO_4 (100 ml), water (2×100 ml), saturated aqueous $NaHCO_3$ (100 ml) and again with water (2×100 ml), dried over $MgSO_4$ and concentrated. The resulting mixture was chromatographed on a SiO_2 column (dichloromethane). The fractions with R_f 0.76 yielded 0.270 g (4%) of **5**. The fraction with R_f 0.45 was evaporated and the residue recrystallized from toluene (under argon) to give 3.71 g (62%) of unreacted 4-hydroxy[2.2]paracyclophane. Racemic (*R**,*R**)-bis[5-(4-hydroxy[2.2]paracyclophanyl)]-methane (*R**,*R**)-**6** (0.6 g, 10%) was isolated as a colorless crystalline material from the fractions with R_f 0.625 (CH_2Cl_2). An analytically pure sample was obtained by recrystallization from ethanol. ^{1}H NMR ($CDCl_3$; δ, ppm; J, Hz): 2.45–3.65 (m, 16H, -C**H**$_2$-C**H**$_2$-); 3.18 (s, 2H, -C**H**$_2$-); 4.7 (s, 2H, -O**H**); 6.28 (d, 2H, ^{3}J = 7.8); 6.39 (d, 2H, ^{3}J = 7.8); 6.46 (dd, 2H, ^{3}J = 7.8, ^{4}J = 1.8); 6.56 (dd, 2H, ^{3}J = 7.8, ^{4}J = 1.8); 6.73 (dd, 2H, ^{3}J = 7.8, ^{4}J = 1.8); 6.86 (dd, 2H, ^{3}J = 7.8, ^{4}J = 1.8). ^{13}C NMR ($CDCl_3$; δ, ppm): 27.98, 29.84, 33.57, 33.67, 34.37, 125.28, 126.95, 127.09, 127.14, 127.28, 132.44, 133.21, 133.40, 137.83, 139.22, 139.50, 153.34. MS (EI, 70 eV), *m*/*z*, ($I_{rel.}$%): 460 (32), 356 (20), 355 (33), 252 (15), 251 (44), 237 (59), 120 (52), 104 (100). Mp 225.5–228°C (decomp.). Found (%): C 85.93; H 7.15. $C_{33}H_{32}O_2$. Calculated (%): C 86.05; H 7.00.

4.5. *Racemic 4-hydroxy-5-hydroxymethyl[2.2]paracyclophane* rac-**9**

$LiAlH_4$ (0.090 g, 2.368 mmol) was added to a solution of *rac*-**5** (0.200 g, 0.793 mmol) in anhydrous ether (40 ml). The reaction mixture was stirred at room temperature until the solution became colorless (1.5 h) and then acidified with 10% aq. H_2SO_4 until the precipitate entirely dissolved. The organic phase was separated and the aqueous phase was extracted with Et_2O (2×15 ml). The combined organic phase was washed with water (2×20 ml), saturated aq. Na_2CO_3 solution (20 ml), again water (15 ml) and finally dried over Na_2SO_4. The solvent was evaporated under reduced pressure; the solid residue was dried for 6 h in vacuo to afford 0.198 g (98%) of *rac*-**9**. An analytically pure sample of *rac*-**9** was prepared by crystallization from heptane under argon in a yield of 0.161 g (80%). R_f 0.38 (SiO_2, ether:benzene (1:5)). ^{1}H NMR ($CDCl_3$; δ, ppm; J, Hz): 1.86 (dd, 1H, -CH_2O***H***, ^{3}J = 8.1, ^{3}J = 3.4); 2.62 (m, 1H, -CH_2-CH***H***-); 2.77 (m, 2H, -C***H***$_2$-C***H***$_2$-); 3.08 (m, 4H, -C***H***$_2$-C***H***$_2$-); 3.37 (m, 1H, -CH_2-CH***H***-); 4.46 (dd, 1H, -CH***H***OH, ^{2}J = 12.8, ^{3}J = 8.1); 4.73 (dd, 1H, -CH***H***OH, ^{2}J = 12.8, ^{3}J = 3.4); 6.2 (d, 1H, 7.5); 6.44 (d, 1H, 7.5); 6.48 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8); 6.55 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8); 6.57 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8); 6.89 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8); 7.24 (s, 1H, -O***H***). Mp 147–153°C. Found (%): C 80.15; H 7.22. $C_{17}H_{18}O_2$. Calculated (%): C 80.29; H 7.22.

4.6. *(S)-4-Hydroxy-5-hydroxymethyl[2.2]paracyclophane (S)-**9***

The reduction of (*S*)-**5** (0.640 g, 2.54 mmol) with $LiAlH_4$ (0.290 g, 7.63 mmol) in anhydrous ether (120 ml) was carried out similarly to the reduction of *rac*-**5**, to give (*S*)-**9** (0.632 g) in a 98% yield. NMR spectra of the compound were identical to those of *rac*-**9**. Mp 147–153°C, $[\alpha]_D^{25}$ –173.3 (*c* = 0.2, benzene). Found (%): C 80.19; H 7.20. $C_{17}H_{18}O_2$. Calculated (%): C 80.29; H 7.22.

4.7. *(S,S)-Bis[5-(4-hydroxy[2.2]paracyclophanyl)]methane (S,S)-**6** (similar procedure was used for the synthesis of* rac-**6**)

A mixture of magnesium turnings (0.200 g, 8.23 mmol) and anhydrous methanol (20 ml) was kept under argon until hydrogen evolution ceased (~1.2 h). A portion of the resulting solution of

magnesium methoxide (10 ml) was added in an Ar flow to *rac*-**4** (1.59 g, 7.09 mmol). The reaction mixture was kept at 50–60°C for 1 h and allowed to cool down to room temperature, then the solvent was removed under reduced pressure, anhydrous toluene (50 ml) was added in an argon flow and the mixture was heated to 75°C over a period of 15 min and cooled to room temperature. Compound (*S*)-**9** (0.600 g, 2.36 mmol) and toluene (3 ml) were added, the reaction mixture was kept at 105–110°C under argon for 2 h and cooled to room temperature. Toluene (~25 ml) was evaporated in vacuo over a period of 1 h. A fresh portion of toluene (25 ml) was added and the reaction mixture was kept at 105–110°C for 3 h, cooled to room temperature, acidified with 30 ml of aq. H_2SO_4 (1:10) and vigorously stirred for 1 h at 30°C. The organic phase was separated and the aqueous layer extracted with toluene (3×30 ml) and then ether (3×30 ml). The combined organic phase was washed with 50 ml of a saturated aqueous solution of Na_2CO_3 (2×10 ml) and water (2×40 ml) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue separated on a SiO_2 column (CH_2Cl_2). Chromatographically pure (*S*,*S*)-**6** (0.347 g, 32%) was isolated from the fraction with R_f 0.49 (CH_2Cl_2). The yield of (*S*,*S*)-**6** after recrystallization from ethanol in a flow of dry argon was 0.326 g (30%). NMR spectra of the compound were identical to those of (*R**,*R**)-**6**. Mp (decomp.) 225.5–228°C . $[\alpha]_D^{25}$ –198.6 ($c = 1.02$, THF). Found (%): C 86.06; H 7.00. $C_{33}H_{32}O_2$. Calculated (%): C 86.05; H 7.00.

4.8. Racemic [5-(4-hydroxy[2.2]paracyclophanyl)-2-(3,6-dimethyl)hydroxyphenyl)]methane **12**

2,5-Dimethylphenol **10** (0.130 g, 1.06 mmol) was made to react with *rac*-**9** (0.090 g, 0.354 mmol) according to the same procedure (see above). The organic phase was separated. The aqueous layer was extracted with toluene (3×15 ml) and ether (3×15 ml). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (40 ml) and then water (20 ml). The aqueous phases were combined, solid $NaHCO_3$ added to neutralize the solution and the product extracted with THF (3×30 ml). The combined organic phase was dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The solid residue was separated on a SiO_2 column (THF:petroleum ether (1:5). Chromatographically pure bridged biphenol **12** (0.096 g, 76%) was isolated from the fraction with R_f 0.41 upon removal of the solvent under reduced pressure and then removal of the traces of remaining **10** by evacuation of the sample over activated charcoal in vacuo. An analytically pure *rac*-**12** was prepared by recrystallization from ethanol in a flow of dry argon. ^{1}H MR (THF-d_8; δ, ppm; J, Hz): 2.22 (s, 3H, -C***H***$_3$); 2.29 (s, 3H, -C***H***$_3$); 2.55–2.70 (m, 1H, -CH$_2$-CH***H***-);2.80–3.50 (m, 6H, -C***H***$_2$-CH***H***-); 3.56 (d, 1H, -CH***H***-, 14.6); 3.58–3.67 (m, 1H, -CH$_2$-CH***H***-); 3.75 (d, 1H, -CH***H***-, 14.6); 6.31 (d, 1H, ^{3}J = 7.8); 6.40 (d, 1H, ^{3}J = 7.8); 6.53 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8); 6.56 (d, 1H, ^{3}J = 7.8); 6.65 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8); 6.82 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8); 6.85 (d, 1H, ^{3}J = 7.8); 7.04 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8); 8.06 (br.s, 1H, -O***H***); 8.20 (br.s, 1H, -O***H***). MS (EI, 70 eV), *m*/*z*, ($I_{rel.}$%): 358 (14, M^+), 343 (34, M–Me), 341 (16, M–OH), 254 (40, M–*p*-xylylene), 253 (91, M–*p*-xylylene+H), 252 (13), 240 (21), 239 (100, M–*p*-xylylene and Me), 238 (23), 237 (45, M–xylylenol), 236 (41, M–*p*-xylylene and H_2O), 235 (20), 224 (16), 223 (8), 221 (15), 135 (12), 134 (9), 120 (23), 104 (73). Mp (decomp.) 255–280°C. Found (%): C 83.03; H 7.24. $C_{25}H_{26}O_2$. Calculated (%): C 83.76; H 7.31.

4.9. Racemic [5-(4-hydroxy[2.2]paracyclophanyl)-2-(3-isopropyl-6-methylhydroxyphenyl)]methane **13**

2-Isopropyl-5-methylphenol **11** (0.160 g, 1.06 mmol) was made to react with *rac*-**9** (0.090 g, 0.354 mmol) according to the procedure described for the synthesis of **6**. The organic layer was separated. The aqueous layer was extracted with toluene (3×15 ml) and ether (3×15 ml). The

combined organic solution was washed with a saturated aqueous solution of $NaHCO_3$ (40 ml) and water (20 ml) and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was separated on a SiO_2 column (THF:petroleum ether, 1:5). Chromatographically pure racemic bridged biphenol **13** (0.096 g, 70%) was isolated from a fraction with R_f 0.45 (THF:petroleum ether, 1:5) upon removal of the solvent under reduced pressure and then removal of the traces of remaining **11** by evacuation of the sample over activated charcoal in vacuo. An analytically pure sample was prepared by recrystallization from ethanol in a flow of dry argon. ^{1}H NMR ($CDCl_3$; δ, ppm; J, Hz): 1.21 (d, 3H, -CH(C***H***$_3$)$_2$, 6.9); 1.23 (d, 3H, -CH(C***H***$_3$)$_2$, 6.9); 2.22 (s, 3H, -C***H***$_3$); 2.50–2.70 (m, 1H, -CH$_2$-CH***H***-); 2.80–3.30 (m, 7H, -C***H***$_2$-C***H***$_2$-); 3.49 (d, 1H, -CH***H***-, ^{2}J = 15.3); 3.50 (m, 1H, -C***H***(CH$_3$)$_2$); 3.65 (d, 1H, -CH***H***-, ^{2}J = 15.3); 6.03 (br.s, 2H,-O***H***); 6.30 (d, 1H, ^{3}J = 7.8); 6.38 (d, 1H, ^{3}J = 7.8); 6.48 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8); 6.58 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8); 6.68 (d, 1H, ^{3}J = 7.8); 6.77 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8); 6.93 (d, 1H, ^{3}J = 7.8); 6.97 (dd, 1H, ^{3}J = 7.8, ^{4}J = 1.8). MS (EI, 70 eV), *m*/*z*, ($I_{rel.}$%): 386 (14, M^+), 371 (44, M–Me), 369 (13, M–OH), 343 (27, M–Pr), 282 (35, M–*p*-xylylene), 281 (89), 267 (65, M–*p*-xylylene and Me), 240 (56), 239 (67, M–*p*-xylylene and Pr), 239 (42), 238 (30), 225 (37), 224 (33), 223 (21), 221 (24), 163 (18), 149 (12), 150 (12), 104 (100). Mp (decomp.) 229.5–253°C. Found (%): C 83.46; H 7.83. $C_{27}H_{30}O_2$. Calculated (%): C 83.90; H 7.82.

*4.10. Formylation of a mixture of 4-hydroxy[2.2]paracyclophane **4** with* meso-*bis[5-(4-hydroxy-[2.2]paracyclophanyl)]methane* meso-***6***

Bu_3N (0.816 g, 1.05 ml, 4.41 mmol) and $SnCl_4$ (0.297 g, 0.133 ml, 1.13 mmol) were added to a solution containing a mixture of **4** and (*S*,*R*)-**6** (1.41 g) in anhydrous toluene (70 ml) and the reaction mixture was stirred for 0.5 h, then $(CH_2O)_n$ (0.755 g, 25.2 mmol) was added and the mixture was kept at 100°C. After 2 h the reaction vessel was cooled to room temperature and a new portion of Bu_3N (0.816 g, 1.05 ml, 4.41 mmol), $SnCl_4$ (0.297 g, 0.133 ml, 1.13 mmol) and $(CH_2O)_n$ (0.755 g, 25.2 mmol) added. The reaction mixture was kept for 2 h at 100°C, cooled to room temperature and acidified with 2N HCl (20 ml). The organic layer was separated; the aqueous layer extracted with toluene (3×30 ml). The combined organic fraction was dried over Na_2SO_4 and evaporated, the residue was purified by chromatography on a SiO_2 column (toluene) to afford 0.12 g of **5** (R_f = 0.6, toluene), $[\alpha]_D^{25}$ +62 (*c* = 0.42, benzene). The *meso*-**6** and unreacted **4** could be recovered from the column by elution with THF.

*4.11. Preparation of the di(isopropyloxy)titanate of (*S,S*)-bis[5-(4-hydroxy[2.2]paracyclophanyl)]-methane (*S,S*)-**6***

Toluene (4 ml) and Ti(O^{i}Pr)$_4$ (0.18 ml, 0.6 mmol) were added to (*S*,*S*)-**6** (0.23 g, 0.5 mmol) under Ar. The resulting orange colored solution was stirred for 5 h at room temperature. The toluene and *i*-PrOH liberated upon ligand exchange were removed in vacuo at room temperature and the residue was dried in vacuo.

4.12. Enantioselective addition of diethylzinc to benzaldehyde

Benzaldehyde (0.35 g, 0.34 ml, 3.3 mmol) was added to a stirred solution of di(isopropyloxy)-titanate of (*S*,*S*)-**6** (0.15 equiv., 0.5 mmol) and Ti(O^{i}Pr)$_4$ (0.85 g, 0.9 ml, 3.0 mmol) in toluene (10 ml). The resulting yellow solution was cooled to –25°C and a toluene solution of Et_2Zn (2.25 ml,

4.5 mmol) was added. The reaction mixture was stirred for 15 h at –25°C. After hydrolysis with 8 ml of a saturated solution of NH_4Cl, the mixture was allowed to warm up slowly to a room temperature and filtered. The solid residue was washed with 10 ml of ether. The organic phase was separated and the aqueous layer was extracted with 2×20 ml of ether. The combined organic phase was dried over $MgSO_4$ and concentrated. Then pentane (15 ml) was added and (*S*,*S*)-**6** (0.22 g, 95%) was separated by filtration. After evaporation of pentane, the mixture was examined by ^1H NMR, that showed the absence of even traces of the starting benzaldehyde. The enantiomeric purity of 1-phenyl-1-propanol was determined by chiral GLC.

The modified reaction without any excess of $Ti(O^iPr)_4$ added to the catalyst (Table 1, run 2) was carried out and analyzed in the same manner as described above.

Acknowledgements

Financial support of this work by INCO-COPERNICUS IC-15-CT960722 and Russian Science Foundation (grant Ref. N 97-03-32972a, 00-03-32840a and 00-15-97359) are gratefully acknowledged. The work of Ph.D. student R. Zhuravsky was supported by the Scientific Training Center of Chemistry of Organometallic Compounds (grant 234, the Federal Target Program 'Integration').

References

1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995; Narasaka, K. *Synthesis* **1991**, 1–10; Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503–517.
2. (a) Yamamoto, K.; Fukushima, H.; Nakazaki, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1490–1491; (b) Reetz, M.; Merk, C.; Mehler, G. *J. Chem. Soc., Chem. Commun.* **1998**, 2075–2076.
3. *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Materials Science*; Hayashi, T., Ed.; VCH: Weinheim, 1995; Togni, A. *New Chiral Ferrocenyl Ligands for Asymmetric Catalysis*; Togni, A.; Halterman, R. L., Eds. Metallocenes. Wiley-VCH: Weinheim, 1998; Vol. 2, pp. 685–721.
4. Antonov, Yu. D.; Belokon', Yu. N.; Ikonnikov, N. S.; Orlova, S. A.; Pisarevsky, A. P.; Raevsky, N. I.; Rozenberg, V. I.; Sergeeva, E. V.; Struchkov, Yu. T.; Tararov, V. I.; Vorontsov, E. V. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1873–1879; Belokon', Yu.; Moscalenko, M.; Ikonnikov, N.; Yashkina, L.; Antotov, D.; Vorontsov, E.; Rozenberg, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3245–3250; Pye, P.; Rossen, K.; Reamer, R.; Tsou, N.; Volante, R.; Reider, P. *J. Am. Chem. Soc.* **1997**, *119*, 6207–6208; Pelter, A.; Kidwell, H.; Crump, R. A. N. C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3137–3139; Fringueli, F.; Permitti, O.; Pizzo, F.; Ruzzioni, R. *Chem. Lett.* **2000**, *2*, 38–39.
5. (a) Nesmeyanov, A. N.; Sazonova, V. A.; Drozd, V. D. *Dokl. Akad. Nauk USSR* **1959**, *129*, 1060–1063; (b) Khorn, K.; Reiger, H.; Hopf, H.; Barrett, D.; Jones, P. G.; Doring, D. *Chem. Ber.* **1990**, *B. 123*, 1729–1732; (c) Vögtle, F. *Cyclophane Chemistry*; John Wiley & Sons: Chichester, New York, Brisbane, Toronto, Singapore, 1993; pp. 71–112.
6. Aldred, R.; Johnston, R.; Lewin, D.; Neilan, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1823–1831.
7. Rozenberg, V.; Kharitonov, V.; Antonov, D.; Sergeeva, E.; Aleshkin, A.; Ikonnikov, N.; Orlova, S.; Belokon' Yu. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 91–92; Hopf, H.; Barrett, D. *Liebigs Ann.* **1995**, 449–451; Capiciani, A.; Fringuelli, F.; Mancini, V.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. *J. Org. Chem.* **1997**, *62*, 3744–3747.
8. Casiraghi, G.; Casnati, G.; Cornia, M.; Pochini, A.; Puglia, G.; Sartori, G.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 318–321.
9. Casnati, G.; Casiraghi, G.; Pochini, A.; Sartori, G.; Ungaro, R. *Pure Appl. Chem.* **1983**, *55*, 1677–1688.
10. Pochini, A.; Ungaro, R. *Synthesis* **1978**, 617–619; Casiraghi, G.; Casnati, G.; Cornia, M.; Pochini, A.; Sartori, G.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 322–325.
11. Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363–4384.
12. Sheldrick, G. M. SHELXTL PC Version 5.0. An integrated system for solving, refining and displaying crystal structures from diffraction data. Siemens Analytical X-ray Instruments Inc.: Madison, WI, 1994.