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Symmetrically Tetrasubstituted [2.2]Paracyclophanes: Their Systematization and Regioselective Synthesis of Several Types of Bis-Bifunctional Derivatives by Double Electrophilic Substitution

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Abstract: The possible number of chiral and achiral tetrasubstituted [2.2]paracyclophanes possessing different types of symmetry (C_2, C_i, C_s, C_{2v}, C_{2h}) is evaluated and a unified independent trivial naming descriptor system is introduced. The reactivity and regioselectivity of the electrophilic substitution of the chiral pseudo-*meta*- and achiral pseudo-*para*-disubstituted [2.2]paracyclophanes are investigated in an approach suggested to be general for the synthesis of bis-bifunctional [2.2]paracyclophanes. The mono- and diacylation of chiral pseudo-*meta*-dihydroxy[2.2]paracyclophane **14** with acetylchloride occur *ortho*-regioselectively to produce tri- **22**, **23** and symmetrically **21** tetrasubstituted acyl derivatives. The same reaction with benzoylchloride is neither regio-, nor chemoselective, and gives rise to a mixture of *ortho*-/*para*-, mono-/diacylated compounds **27**–**31**. The double acylation of pseudo-*meta*-dimethoxy[2.2]paracyclophane **18** is completely *para*-regioselective. Electrophilic substitution of pseudo-*meta*-bis(methoxycarbonyl)-[2.2]paracyclophane **20** regioselectively generates the pseudo-*gem*-substitution pattern. Formylation of this substrate produces the monocarbonyl derivatives **35** only, whereas the Fe-catalyzed bromination may be directed towards mono- **36** or disubstitution **37** products chemoselectively by varying the reactions conditions. The diacylation and dibromination reactions of the respective achiral diphenol **12** and bis(methoxycarbonyl) **40** derivatives of the pseudo-*para*-structure retain regioselectivities which are characteristic for their pseudo-*meta*-regioisomers. Imino ligands **26**, **25**, and **39**, which were obtained from monoacyl- **22** and diacyldihydroxy[2.2]paracyclophanes **21**, **38**, are tested as chiral ligands in stereoselective Et_2Zn addition to benzaldehyde producing 1-phenylpropanol with *ee* values up to 76%.

Keywords: asymmetric catalysis · cyclophanes · electrophilic substitution · regioselectivity · resolution

Introduction

Ever since [2.2]paracyclophane (**1**) was first prepared by Brown and Farthing nearly 60 years ago[1] this prototypical layered organic molecule (and as such the sister molecule of layered metal organic compounds: ferrocene) has attracted the interest of numerous chemists. Whereas during the first part of the history of this remarkable three-dimensional aromatic compound preparative, structural and spectroscopic questions stood in the foreground of research, in more recent times a shift of interest towards application of **1** and its derivatives—often in areas far apart from synthetic chemistry—is discernible. For example[2] the use of cyclophanes in materials chemistry and asymmetric catalysis are present-day central topics in the field. The bonding of two

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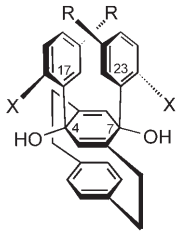
parallel benzene rings in close proximity provides three-dimensional (3D) structures with unique electronic properties, extremely useful for the design of new materials fulfilling the requirements of nonlinear optics, optoelectronics, chemical sensing materials,[3] liquid crystallinity,[4] and photoluminescent conjugated polymers.[5] Substituted [2.2]paracyclophanes treated under chemical vapor deposition (CVD) conditions furnish poly-*para*-xylylene films which impart useful properties to the coated surface.[6] At the same time the planar chirality of cyclophanes, connected with high thermal (up to 200 °C) and chemical stability (towards the action of acids and bases), has proven useful for the construction of a variety of efficient chiral ligands.[7]

Up to now the majority of the investigations in all these areas were carried out with mono- and disubstituted paracyclophanes whereas the share of tri-, tetra- and polysubstituted derivatives was meagre. One of the possible reasons is the absence of convenient techniques to prepare the respective compounds. Tetrasubstituted [2.2]paracyclophanes are commonly approached in two general ways based on the formation of the cyclophane scaffold: i) by the well-elaborated dithiacyclophane route, that is, the initial synthesis of 2,11-dithia[3.3]paracyclophanes already bearing the substituents in appropriate positions of the aromatic rings,[8] followed by sulfur extrusion via pyrolysis[9a] or photolysis[9b] or, ii) by the Diels–Alder cycloaddition of 1,2,4,5-hexatetraenes with symmetrically or unsymmetrically substituted acetylenes[10] producing, as a rule, mixtures of regioisomers. Another approach is based on polysubstitution of [2.2]paracyclophane (**1**) itself, such as, for example, direct tetrabromination with Br_2 (cat. Fe),[11a] in liquid Br_2 (cat. I_2),[11b] or a sonication-assisted tetrabromomethylation,[3c] producing in each case mixtures of chiral and achiral derivatives (see below), respectively. Further stepwise substitution of these brominated homo-tetrasubstituted paracyclophanes gave rise to a number of regioisomeric two-donor/two-acceptor derivatives.[3c] It is clear that all these approaches suffer from poor regioselectivity. Only very recently has the improved Hofmann 1,6-elimination technique been suggested as a regioselective route to synthesize several symmetrical di-, tetra-, and octasubstituted [2.2]paracyclophane derivatives, as well as the parent hydrocarbon itself.[12]

In our line of research, polysubstituted [2.2]paracyclophane derivatives would be a further contribution to a study of [2.2]paracyclophanes of variable structure applicable as planar chiral ligands in asymmetric catalysis,[13] as monomers for poly-*para*-xylylene film synthesis[14] or for the investigation of liquid crystalline properties.[4] As the first example of multichiral C_2-symmetric bis-bifunctional [2.2]paracyclophanes, diastereomerically and enantiomerically pure cyclohexadienones (R_p,4R_c,7R_c,4,23R_a,7,17R_a)-*cis*-4,7-diarylsubstituted-4,7-dihydroxy-4,7-dihydro[2.2]paracyclophanes (**2**), which possess elements of planar, central and axial chirality, Figure 1) were recently synthesized by us via a stereospecific reaction of *ortho*-substituted aryllithium reagents with [2.2]paracyclophane-4,7-quinone.[15]



(R_p,4R_c,7R_c,4,23R_a,7,17R_a)-**2**

Figure 1. Bis-bifunctional cyclohexadienols **2**.

In such ligands the hydroxy groups, bound to the [2.2]paracyclophane scaffold and arranged pairwise with functional groups of the aryl fragments, form two independent systems, both of which are capable of coordination with a metal or metal containing fragment. These compounds function as chiral inductors in the enantioselective addition of diethylzinc to benzaldehyde (up to 93.5 % *ee*).[15b]

Among other synthetic techniques applied for the synthesis of tetrasubstituted [2.2]paracyclophanes, little attention has so far been paid to an approach that is very attractive from the synthetic point of view: the double electrophilic substitution of suitably disubstituted [2.2]paracyclophanes (possessing two identical functional groups), allowing the one-step introduction of a pair of two other identical functional groups and thus the synthesis of symmetrical tetrasubstituted compounds. This approach is illustrated in the literature by isolated examples only so far, for example *para*-regioselective dibromination of pseudo-*ortho*-dibromo-[2.2]paracyclophane and *ortho*-regioselective dibromination of pseudo-*para*-dibromo[2.2]paracyclophane,[11a] pseudo-*gem*-regioselective double chloromethylation of *para*-bis(methoxycarbonyl)[2.2]paracyclophane,[16] *ortho*-regioselective double acylation of pseudo-*ortho*-dihydroxy-[2.2]paracyclophane (PHANOL), and *para*-regioselective chlorosulfonation of its diacetate.[17] Dinitration of pseudo-*ortho*-dibromo[2.2]paracyclophane is also *para*-regioselective,[17] whereas acylation, oxaloylation, and formylation of this substrate *para*-regioselectively produce the monocarbonyl compounds only.[18] A single example of pseudo-*gem*-regioselective bromination of unsymmetric 4-bromo-5-diethylcarbamoyl[2.2]paracyclophane is also known.[19]

Here we present the first direct electrophilic substitution of C_2-symmetrical chiral pseudo-*meta*-[20] and C_i-symmetrical achiral pseudo-*para*-disubstituted [2.2]paracyclophanes as an approach to the chemo- and regioselective synthesis of tetrasubstituted [2.2]paracyclophanes. We also have evaluated the number of all possible symmetrical tetrasubstituted [2.2]paracyclophanes containing substituents in their aromatic rings, describe their symmetry properties, and introduce a convenient descriptor system for naming them. First results of the usage of some polysubstituted [2.2]paracyclophanes as chiral inductors in asymmetric catalysis are also reported.

Results and Discussion

Statement of the problem: The rapid progress in preparative [2.2]paracyclophane chemistry has brought forth a large number of differently polysubstituted [2.2]paracyclophanes, among which those with four aromatic substituents in a symmetrical substitution pattern have attracted the interest of chemists because of their possible use in various areas of modern chemistry (see below: Prospects). Such symmetrical compounds could possess very diverse substitution patterns, either chiral or achiral, homo- or heterosubstituted, and comprise in their structures two chemically and, in the case of chiral compounds stereochemically identical functional units. We suggest to designate them as bis-bifunctional [2.2]paracyclophanes (Figure 2). In our opinion, one of the more important questions is the proper description of the array of substituents in these derivatives.

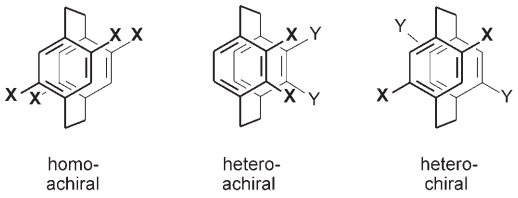


Figure 2. Examples of bis-bifunctional [2.2]paracyclophanes.

Such an extension is necessary since at least three different nomenclature systems are used in the present chemical literature for the naming of [2.2]paracyclophane derivatives. In all these systems the numbering of the bridge carbon atoms and of the aromatic carbons of the first ring are the same and accepted as originally proposed by Cram[21] (Figure 3). These systems differ, however, as to how the carbon atoms should be numbered in the second ring. Thus, in the first numbering scheme the front-side (facing) carbon atoms of each aromatic ring of the [2.2]paracyclophane molecule have lower numbers than their respective back-side atoms (Figure 3, left structure **3**).[13,19,22,23] Working on the numbering of multibridged [2$_n$]cyclophanes, Boekelheide[24a] suggested to number all carbons in aromatic rings in a clockwise manner, starting each time from the nearest bridgehead (Figure 3, right structure **3**). In the case of [2.2]paracyclophane this leads to a situation, in which the back-side carbon atoms of the upper ring now carry the lower numbers.[24b] These two nomenclature systems hence give dissimilar names to compound of type **3** (which is either a 4,16- or a 4,12-disubstituted [2.2]paracyclophane). The other commonly used system[8,9,25,26] numbers carbon atoms in the second ring by ascribing the lower number to the substituent-carrying carbon atoms. However, this system does not allow one to distinguish between the front and back sides of the molecule and, consequently, to describe properly the respective regioisomers (for example, both **3** and **4** would be 4,12-disubstituted in this case (Figure 3, right).

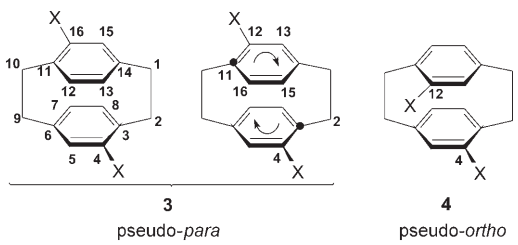


Figure 3. Different nomenclature systems commonly used for numbering of [2.2]paracyclophane derivatives.

The recently recommended IUPAC Phane Nomenclature[27a,b] which demands the use of the lowest locants rule[27c] in numbering of the respective substituents attached to the simplified skeleton also does not discern the regioisomers.[27d] For disubstituted [2.2]paracyclophanes, the proper description could be done by using the "pseudo"-prefixes suggested by Cram,[28] which unequivocally define the mutual arrangement of two substituents (for example, disubstituted [2.2]paracyclophanes **3** and **4** would be pseudo-*para*- and pseudo-*ortho*-, respectively, Figure 3).

For tetrasubstituted chiral and achiral derivatives the ambiguities in their description prompted chemists to add different prefixes or epithets to designate the mutual arrangement of the substituents, that we would like to illustrate by selected examples. Thus, structures of both pairs of chiral bis-bifunctional regioisomeric compounds **5** and **6** (4,7-dimethoxy-12,15-dinitro-[9] and 4,7-dicyano-12,15-dimethoxy-,[25] Figure 4, left), were described as pseudo-*ortho*- or "staggered" for **5** and pseudo-*geminal* or "eclipsed" for **6**. On the other hand, homo-tetrasubstituted compounds (achiral **7** and chiral **8**, Figure 4, right) were discerned as either *ortho–ortho*- and *para–para* (R = CH_2Br[3c] or OMe[8,9]) or pseudo-*para* and pseudo-*ortho*- (R = Br).[12] Nevertheless, the usage of such prefixes does not only make the nomenclature system more cumbersome but it also often does not provide an unambiguous representation of the structure.

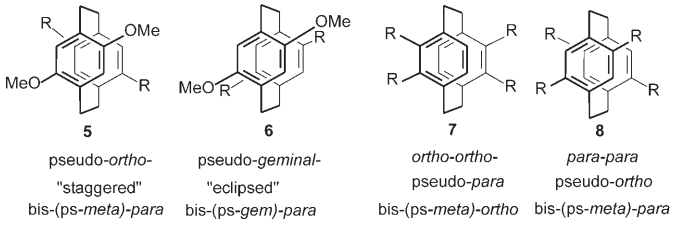


Figure 4. Selected examples of distinguishing between regioisomeric tetrasubstituted [2.2]paracyclophanes.

We have hence decided to develop a unified, comprehensive, and self-consistent descriptor system for the naming of symmetrical tetrasubstituted [2.2]paracyclophane derivatives with substituents in their aromatic rings. As the first step we calculated the possible number of such compounds by a combinatorial approach[29] and found that there could be 28 items: 7 structural isomers with four equal substituents X

(homosubstituted) and 21 isomers with two pairs of different substituents X and Y (heterosubstituted). The second step involves the systematization of these compounds by substitution patterns and types of symmetry. With this aim we approached the tetrasubstituted symmetrical [2.2]paracyclophanes as derivatives of the respective disubstituted [2.2]paracyclophanes of seven possible substitution patterns (three chiral and four achiral).[30] The rule proposed by us for an accurate estimation of the novel patterns (so-called "homonymous substitution" rule) is presented below in detail for chiral compounds and then expanded to respective achiral compounds. The third step consist of the construction of the descriptors for each novel pattern, and for this purpose we have decided to chose the combination of the usual prefixes (*ortho*-, *meta*-, and *para*-) with Cram's "pseudo"-prefixes (pseudo-*ortho*-, pseudo-*meta*-, pseudo-*para*-, and pseudo-*gem*-) which have been accepted and used for a long time in [2.2]paracyclophane chemistry.

Symmetrically tetrasubstituted [2.2]paracyclophane derivatives: symmetry properties and unified descriptor system for their denotation

C_2-Symmetrical chiral tetrasubstituted [2.2]paracyclophanes: The first generation of chiral C_2-symmetrical [2.2]paracyclophanes is presented by derivatives which are X,X-disubstituted in their aromatic rings and belong to three patterns (*para*- (**A**), pseudo-*ortho*- (**B**), and pseudo-*meta*- (**C**), differing in the orientation of the C_2-axis[30] (Figure 5). The next generation of C_2-symmetrical [2.2]paracyclophanes (namely, tetrasubstituted derivatives) arises by heterosubstitution of the parent patterns **A**–**C** (chiral origins) by the pair of substituents Y–Y of the same substitution pattern ("homonymous substitution", namely *para*- (**A**) by *para*-, pseudo-*ortho*- (**B**) by pseudo-*ortho*-, and pseudo-*meta*-substituted pattern (**C**) by pseudo-*meta*- pair Y–Y), and each chiral origin structure **A**–**C** can bind the Y–Y pair in three possible ways. Thus the combination of three disubstituted origins (**A**–**C**) with three possible incoming substitutions leads to the formation of nine tetrasubstituted chiral patterns: **A1**–**A3**, **B1**–**B3**, **C1**–**C3**; within each type the C_2 axis of the parent origin is retained (Figure 5).

Homosubstitution (i.e., by a pair X–X) of each origin, **A**–**C**, produces several additional patterns; however, only one of these, **D** (a superposition of **A2**, **B2**, and **C2**), is chiral and describes the single chiral homo-tetrasubstituted [2.2]paracyclophane of D_3 symmetry[30] (Figure 5).

Symmetrical achiral tetrasubstituted [2.2]paracyclophanes: Apart from ten chiral C_2-symmetrical tetrasubstituted derivatives one can consider 18 additional achiral bis-bifunctional regioisomers. Thus the application of the "homonymous substitution" rule to four achiral origins (*ortho*- (**E**), *meta*- (**F**), pseudo-*gem*- (**G**) of C_s symmetry, and pseudo-*para*- (**H**) of C_i symmetry) produces twelve novel patterns (**E1**–**E3** to **H1**–**H3**) as a result of Y–Y heterosubstitution (Figure 6). Again within each four types the symmetry of the parent origin is retained.

The homonymous X–X homosubstitution of four achiral disubstituted origins **E**–**H** finally gives rise to the next six regioisomers **I**–**N** of C_{2v} and C_{2h} symmetry (Figure 7).

Thus, we have specified all possible patterns of tetrasubstituted symmetrical [2.2]paracyclophanes as 7 homo- and

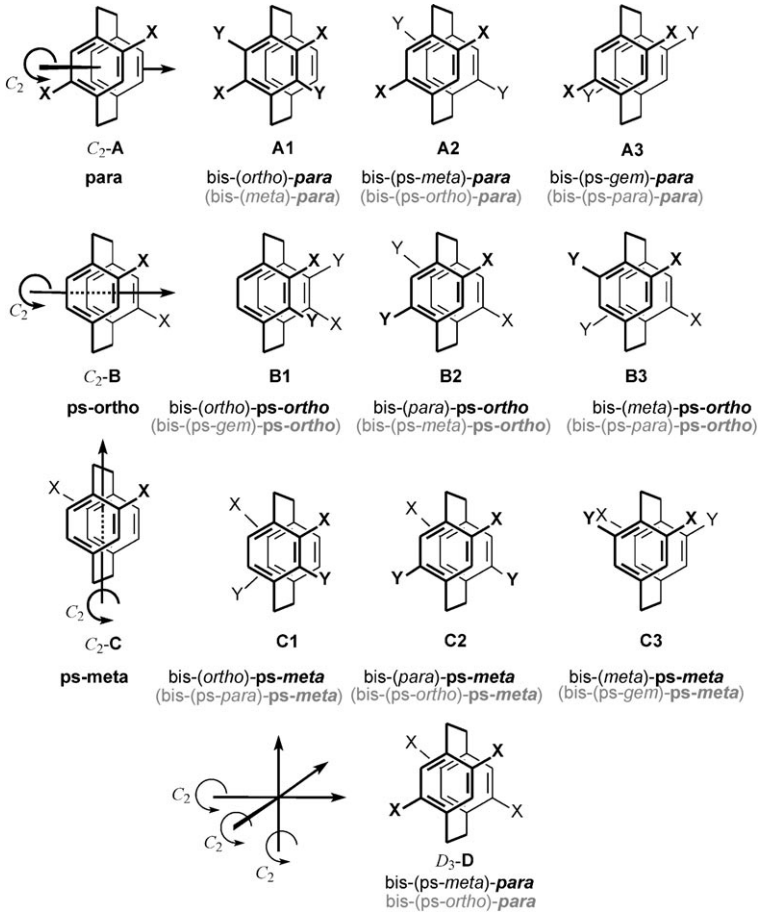


Figure 5. C_2-Symmetrical planar chiral [2.2]paracyclophanes: three disubstituted origins **A**–**C** and ten tetrasubstituted patterns (**A1**–**A3**, **B1**–**B3**, **C1**–**C3**, and **D**) for bis-bifunctional derivatives. In this Figure we will use the prefix "ps-" instead of "pseudo-" for brevity.

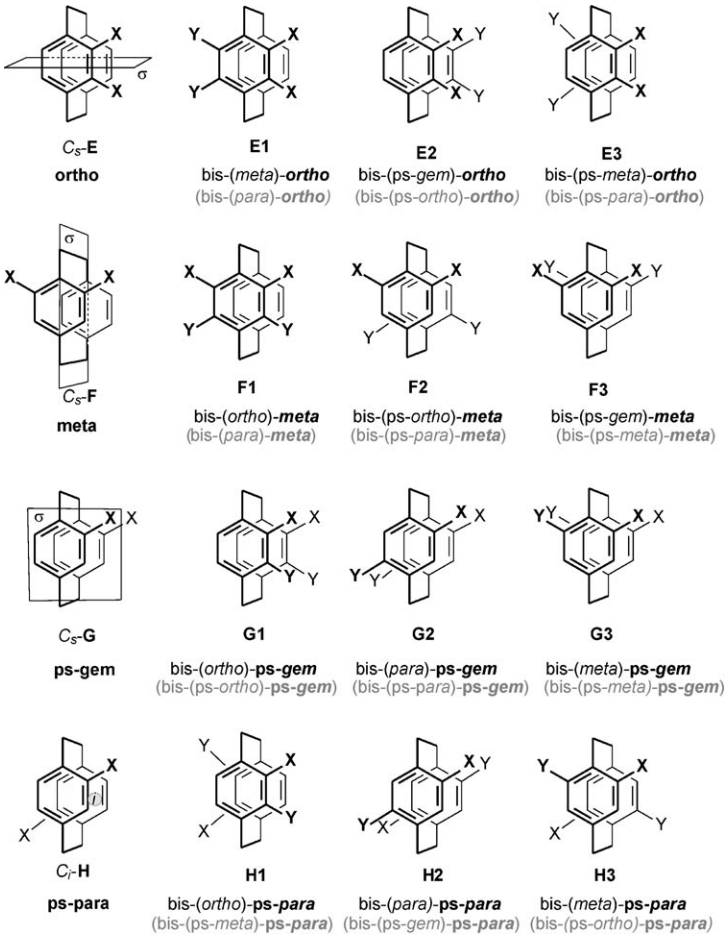


Figure 6. C_s- and C_i-Symmetrical achiral [2.2]paracyclophanes: four achiral disubstituted origins **E**–**H** and twelve novel patterns (**E1**–**E3**, **F1**–**F3**, **G1**–**G3** and **H1**–**H3**) for tetrasubstituted bis-bifunctional derivatives.

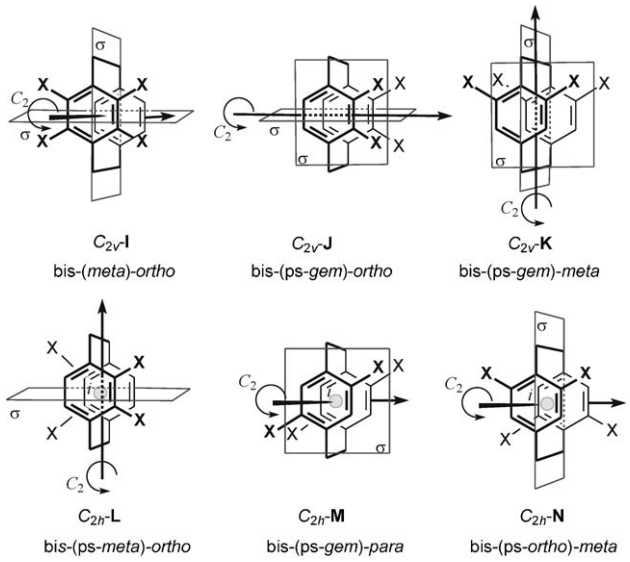


Figure 7. Six patterns of C_{2v}- and C_{2h}-symmetrical achiral homo-tetrasubstituted [2.2]paracyclophanes.

21 heterosubstituted variants, among which 10 are chiral and 18 are achiral.

Construction of the descriptors: In accordance with our proposal, the descriptor for every symmetrical tetrasubstituted [2.2]paracyclophane derivative may be constructed by successive specification of three prefixes chosen from seven possible patterns which describe the relationship between substituents in the molecule of [2.2]paracyclophane (*ortho*-, *meta*-, *para*-, pseudo-*ortho*-, pseudo-*meta*-, pseudo-*para*-, and pseudo-*gem*-). Thus, the descriptor may be constructed by successive specification of three prefixes as follows:

- The first prefix bis- is multiplicative and indicates the presence of two identical pairs of functional groups;
- the last prefix in the sequence denotes the mutual arrangement of these pairs and refers to the positioning of the identical substituents (X vs X and Y vs Y); for C_2-symmetric compounds it always describes a chiral arrangement;
- the middle prefix (in brackets) denotes the relative positions of different substituents in these pairs (X vs Y, the so-called in pair descriptor).

There is a choice to be made between two in pair descriptors possible for each of the structures (for example, *para*- or pseudo-*ortho*- for **C2**, Figure 3). In principle, one may arrive at the drawing of the same structure regardless of which of the two prefixes is used. For the preference we suggest a simple criterion, namely, the shorter path (i.e., smaller number of chemical bonds) from X to Y along the paracyclophane scaffold (which is *para*- in the present example). This preference is related with the lowest locant rule[27c] of IUPAC nomenclature according to which the pair of substituents X and Y of one functional unit would be numbered as 4- and 7- (rather than 4- and 12-). So, the model structure **C2** would be called bis-(*para*)-pseudo-*meta*. However, for the chemists working, for example, in asymmetric synthesis, the other descriptor, namely bis-(pseudo-*ortho*)-pseudo-*meta*, would be more informative, for it displays the location of the functional groups X and Y on the same side of the plane passing through the four bridge carbon atoms and reflects the ability of these groups for coordination. The descriptors for all other chiral and achiral structures are presented in Figures 5 and 6. In two cases only (**F2** and **F3**), when both pairs of prefixes are accountable for equal amounts of chemical bonds, the preference would be made for those, which describe the location of the functional groups X and Y on the same side of the plane passing through the four bridge carbon atoms (pseudo-*ortho*- rather than pseudo-*para*- for **F2** and pseudo-*gem*- rather than pseudo-*meta*- for **F3**).

Homo-tetrasubstituted [2.2]paracyclophanes may be named by choosing the last and the middle prefixes fulfilling the criterion of the shorter X–X path drawn along the paracyclophane scaffold. In this case, the last prefix would always describe the arrangement of two X substituents in

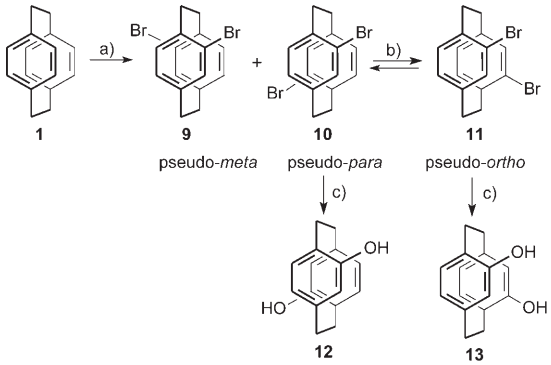
the same aromatic ring and would have preference over the middle prefix in resolving the ambiguous cases. For example, to name structure **I** (with all substituents in the same aromatic ring, Figure 5), one would choose *ortho*- rather than *meta*- or *para*- for the last prefix, and then *meta*- rather than *para*- for the middle prefix. The **K** and **N** regioisomers, with substitution patterns resembled by **F3** and **F2**, respectively, would have their preferable middle prefixes as pseudo-*gem*- and pseudo-*ortho*- in a similar way. The single chiral homosubstituted structure **D** (which resembles **A2**, **B2**, and **C2** at a time) in accordance with the preference criteria could be named as bis-(pseudo-*meta*)-*para* (Figure 5). For the full set of these descriptors see Figures 5–7.

The proposed descriptor system is unified and independent, and so could be used for the naming of all symmetrical tetrasubstituted [2.2]paracyclophanes in addition to any nomenclature. For example, compounds from Figure 4 could be named now as bis-(pseudo-*meta*)-*para* **5**, bis-(pseudo-*gem*)-*para*-**6**, bis-(pseudo-*meta*)-*ortho* **7** and bis-(pseudo-*meta*)-*para* **8**, and as is clear from the Figure, both hetero- and homo-tetrasubstituted paracyclophanes **5** and **8** of the similar substituted pattern have identical descriptors.

It should be noted that the same naming principle may also be applied to a similar classification of bis-trifunctional and bis-tetrafunctional [2.2]paracyclophanes.

Regioselective electrophilic substitution reactions

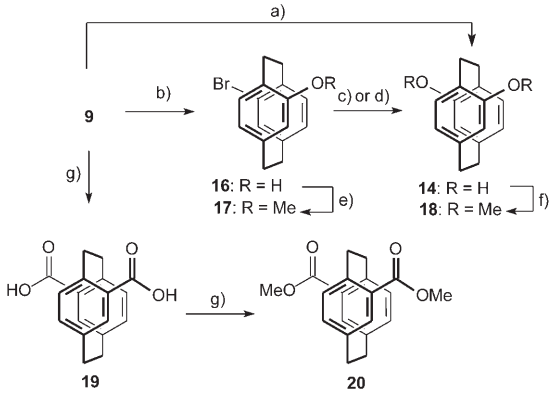
Synthesis of starting materials: As starting materials for the synthesis of pseudo-*para*- and pseudo-*meta*-disubstituted [2.2]paracyclophanes, the respective dibromides were selected. Several years ago we have worked out a non-catalytic dibromination of [2.2]paracyclophane **1** with Br_2 and a separation technique which allowed us to isolate pseudo-*para*-dibromo[2.2]paracyclophane (**10**, 40%) and its pseudo-*meta* isomer (**9**, 10%, Scheme 1).[31] This is in contrast to Cram's Fe-catalyzed dibromination where the respective dibromides **10** (26%) and **11** (pseudo-*ortho*, 16%) were isolated as the main products.[11a] In the present work the pseudo-*meta*-dibromide **9** has been isolated in higher yield (43%) by means of an improved separation procedure (see Experimental Section). Similar bromination and an alternative separation technique, recently described by one of us,[32] yielded the dibromides **9** and **10** in 38 and 31% yield, respectively.



Scheme 1. Non-catalyzed dibromination of [2.2]paracyclophane **1**. a) Br_2, Fe, CCl_4, 98%; b) benzene, 200°C, autoclave 24 h;[13a] c) *n*BuLi, THF, $PhNO_2$.[11a,37]

These simple bromination and separation techniques[31,32] allow to carry out the reaction on a larger scale (up to 25 g per single run), thus making dibromides **9** and **10** readily available for further transformations. Dibromide **10** could also be used for the synthesis of the pseudo-*ortho*-dibromide **11**,[33] a precursor for the paracyclophane derived diphosphine ligand PHANEPHOS, its analogues,[34] and for a number of promising unsymmetrical *N*,*N*-, *N*,*P*-,[35] *N*,*O*-, and *O*,*O*-ligands.[36]

Starting from dibromides **9** and **10** we have carried out the synthesis of several novel as well as already described disubstituted [2.2]paracyclophanes. The choice of functional substituents, attached to the [2.2]paracyclophane scaffold (OH, OMe, and COOMe), was based on known regularities of *ortho*-, *para*-[13d,o] and pseudo-*gem*-regioselective[13k,37] electrophilic substitution, revealed earlier for the monosubstituted [2.2]paracyclophanes. Achiral pseudo-*para*-diphenol **12** was obtained from dibromide **10** in accordance with the described procedure (Scheme 1).[11] For the synthesis of pseudo-*meta*-dihydroxy[2.2]paracyclophane **14** several different transformations were employed (Scheme 2). First, by analogy to the synthesis of the respective pseudo-*para*-dihydroxy- (**12**)[11a] and pseudo-*ortho*-dihydroxy[2.2]paracyclophanes (**13**)[38] we have carried out the double lithiation of dibromide **9** followed by oxidation of the intermediate dilithio derivative with nitrobenzene. This reaction produced the target diphenol **14**, however in low yield (30%), attributable to formation of brownish sticky side products which prevent easy isolation of **14**. The "classical" Li/B exchange with trimethylborate followed by oxidation of the respective boronic esters with H_2O_2/NaOH[39] failed to produce **14**, and



Scheme 2. Synthesis of the starting pseudo-*meta*-[2.2]paracyclophanes. a) 2.4 equiv *n*BuLi, Et_2O, RT, then $PhNO_2$, −78°C; 30%; b) 1.2 equiv *n*BuLi, Et_2O, RT; then $B(OMe)_3$, then H_2O_2/NaOH; 86%; c) 1.2 equiv *n*BuLi, Et_2O, RT; then $B(OMe)_3$, then H_2O_2/NaOH; 87%; d) 1.2 equiv *n*BuLi, THF, −78°C; then $B(OMe)_3$, then H_2O_2/NaOH; 18%; e) NaH/DMF, then MeI, 87%; f) NaH/DMF, then MeI, 80%; g) 2.4 equiv *n*BuLi, Et_2O, RT; then CO_2, then HCl; 74%; h) $SOCl_2$, $CHCl_3$/DMF; then MeOH, 78%.

nothing but parent [2.2]paracyclophane (**1**) and 4-hydroxy-[2.2]paracyclophane (**15**) were isolated from the reaction mixture.

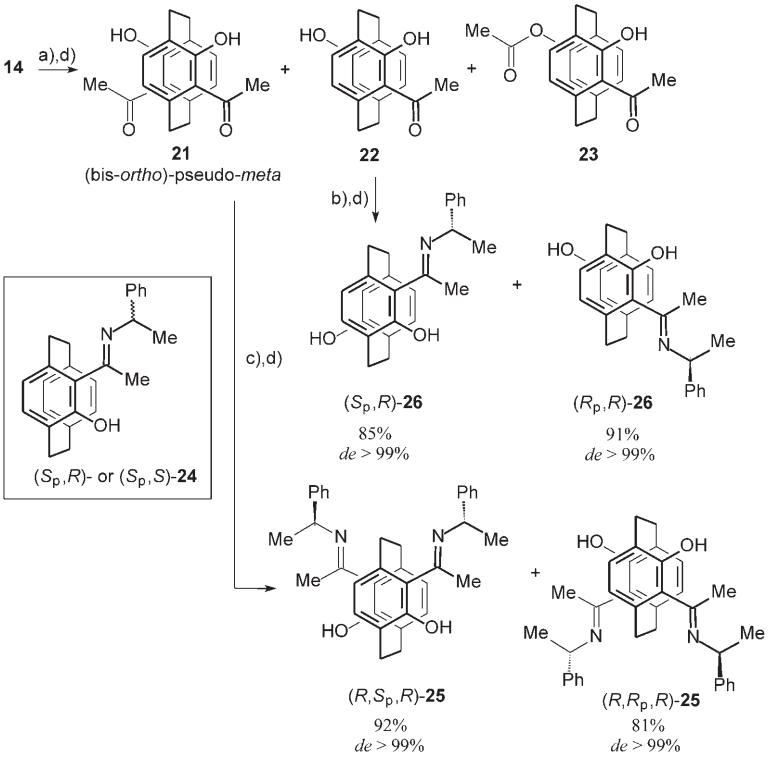
This prompted us to elaborate a stepwise synthetic protocol. Monolithiation of the bromide **9** with *n*BuLi in Et_2O at room temperature, Li/B exchange and oxidation gave rise to 4-bromo-15-hydroxy[2.2]paracyclophane (**16**) in high chemical yield (Scheme 2). Due to difficulties in purification, a portion of the phenol **16** was converted into the respective methyl ether **17**, which was then fully characterized. Crude **16** was again used in the lithiation/electrophilic substitution reaction to produce the target diphenol **14**. Room temperature lithiation in Et_2O has been found more efficient than that at low temperature (−78 °C) in THF (87 vs 18% yield). Diphenol **14** was next transformed into the respective dimethyl ether **18**[23] by a standard methylation procedure. It should be noted that the intermediate brominated monophenol **16** looks very attractive as a starting material for further unsymmetrically disubstituted [2.2]paracyclophanes of the pseudo-*meta* type, as reported earlier for the respective brominated monophenol of pseudo-*ortho*-structure.[34,35]

In contrast to the lack of reactivity of the intermediate dilithio derivative with trimethylborate, its reaction with solid CO_2 (similar to the synthesis of the respective regioisomeric dicarboxylic acids with pseudo-*para*-[40a] and pseudo-*ortho*-arrangement[33b]) occurred smoothly and produced, after acidification of the reaction mixture, pseudo-*meta*-dicarboxy[2.2]paracyclophane (**19**)[41] in high chemical yield (72%, Scheme 2). Dimethyl ester **20** was easily obtained from the diacid **19** through the methoxylation of its respective bis(acidchloride).

***ortho*-Regioselective diacylation of pseudo-*meta*-dihydroxy-[2.2]paracyclophane (14)**: Recently we have found that the $TiCl_4$-catalyzed Friedel–Crafts acylation of 4-hydroxy-[2.2]paracyclophane (**15**) with AcCl and BzCl in dichloromethane, and Fries rearrangement of *O*-acyl-4-hydroxy[2.2]paracyclophane occur *ortho*-regioselectively.[13d] Later Braddock et al. have applied this approach to the acylation of pseudo-*ortho*-diphenol **13** (PHANOL).[17] Various reaction conditions were studied, and it was demonstrated that the double *ortho*-regioselective acylation by valeroyl chloride may be achieved in 1,2-dichloroethane under reflux.

First we examined the acylation of the pseudo-*meta*-diphenol **14** under our standard conditions[13d] with twofold excess of the reagents (3 equiv of AcCl, 3 equiv of $TiCl_4$, CH_2Cl_2, room temperature) and found that three products (*ortho*-structure exclusively) were found in almost equal amounts here, namely, the desired diacylation product: 1,1′-[5,16-dihydroxy[2.2]paracyclophane-4,15-diyl]diethanone (**21**, bis-(*ortho*)-pseudo-*meta*, type **C1**), monoacylated diphenol 1-[5,16-dihydroxy-[2.2]paracyclophan-4-yl]ethanone (**22**), and its *O*-acyl-derivative 16-acetyl-15-hydroxy-[2.2]paracyclophan-4-yl acetate (**23**) (Scheme 3, Table 1, entry 1). Their ratio was determined by ^1H NMR analysis. We have found that larger amounts of the reagents (Table 1, entry 2) and longer reaction times (Table 1, entry 3) affect the product ratio only slightly. Treatment of the reaction mixture with a further portion of the reagents at reflux allowed us to convert **22** into **21**, still producing some of the unfavorable *O*-acylation product **23** (Table 1, entry 4).

Finally the chemoselective synthesis of **21** (93% isolated yield, together with **22** and **23** in trace amounts only) was achieved as follows: a solution of **14** was stirred with $TiCl_4$ for 1 h (to avoid the formation of any *O*-acylation products), then AcCl was added, and the reaction mixture was kept under reflux followed by further addition of the reagents in excess (Table 1, entry 5 and Experimental Section). From the combined reaction mixtures of the unselective reactions (Table 2, entries 1–4) **21**, **22** and **23** have been isolated by preparative chromatography and fully characterized. Addi-



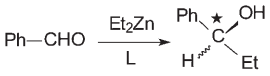
Scheme 3. *ortho*-Regioselective acylation of **14** and synthesis of diastereomeric imino-ligands **25** and **26**. a) 6 equiv AcCl, $TiCl_4$, CH_2Cl_2; b) 1.2 equiv (*R*)-(α)-PEAM, Et_2SnCl_2; c) 2.5 equiv (*R*)-(α)-PEAM, Et_2SnCl_2; d) chromatographic separation.

Table 1. *ortho*-Regioselective mono- and diacylation of diphenol **14** (0.1 M solution in CH_2Cl_2).

Entry	**14**/$TiCl_4$/AcCl ratio, equiv	t_1 [h]	Excess portion of $TiCl_4$/AcCl	t_2 [h]	Ratio of the products **21**/**22**/**23**[d] (chemical yield of **21**)
1[a]	1:3:3	10	–	–	30:35:35
2[a]	1:6:6	10	–	–	40:30:30
3[a]	1:6:6	20	–	–	45:35:20
4[b]	1:6:6	10	6:6	10	60:35:5
5[c]	1:6:6	10	6:6	10	95:3:2 (93%)

[a] Room temperature. [b] $T=40\,°C$. [c] $TiCl_4$ was added to a solution of **14** at RT, the mixture was stirred for 1 h, then AcCl was added and the mixture was kept under reflux ($T=40\,°C$). [d] By ^1H NMR analysis.

Table 2. Asymmetric diethylzinc (2 equiv) addition to benzaldehyde with imino ligands (L, 10 mol%), toluene, 0 °C.



Entry	L	Configuration of 1-phenylpropanol	*ee* [%]
1	(*R*,R_p,*R*)-**25**	(*S*)	36
2	(*R*,S_p,*R*)-**25**	(*R*)	76
3	(R_p,*S*)-**24**	(*S*)	82[41]
4	(S_p,*R*)-**26**	(*S*)	71
5	(*S*,{R_p,S_p},*S*)-**39**	(*S*)	7

tionally for **21** an X-ray investigation was carried out (Figure 8). The presence of only the half set of signals in the ^1H and ^{13}C spectra of **21** reveals the symmetry of the compound. This characteristic spectral feature could be used for identification of all bis-bifunctional [2.2]paracyclophanes.

As is obvious from Figure 8 and Scheme 3, C_2-symmetrical diacylated diphenol **21** comprises two chemically and stereochemically identical units with mutual pseudo-*meta* orientation, both of which mimic the functional part of the 5-acetyl-4-hydroxy[2.2]paracyclophane (AHPC),[13d] a well known precursor for a series of efficient imino-type ligands like **24**.[42] This structural similarity prompted us to obtain bis-bifunctional analogues of the imino-ligands **24**.

Thus the diastereomeric Schiff bases **25** were obtained (85% chemical yield, Scheme 2) from racemic bis-(*ortho*)-pseudo-*meta* **21** and (*R*)-(α)-phenylethylamine ((*R*)-(α)-PEAM). (*R*,R_p,*R*)- And (*R*,S_p,*R*)-**25** were separated by preparative chromatography (*de* >99% by ^1H NMR analysis). For the latter diastereomer (which is less soluble and possesses higher chromatographic mobility in toluene/EtOH) an X-ray diffraction study was carried out (Figure 9); it allowed us to establish the absolute configurations of this diastereomers as (*R*,S_p,*R*)-**25**.

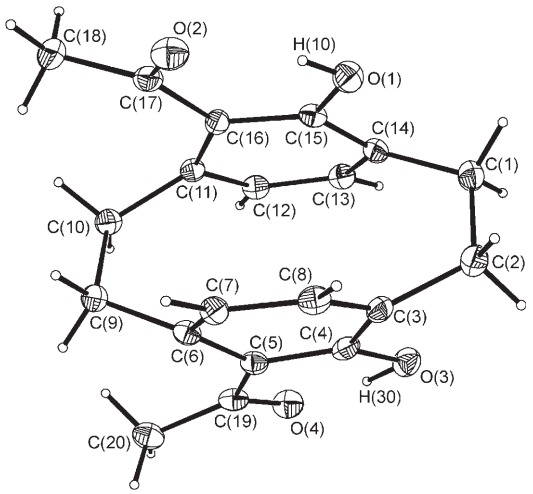


Figure 8. X-ray crystal structure of **21.** Parameters of hydrogen bonds: O(1)-H(10)···O(2) 1.76 Å, O(1)···O(2) 2.522 (2) Å, ∢: O(1)H(10)O(2) 148°; O(3)-H(30)···O(4) 1.73 Å, O(3)···O(4) 2.491 (3) Å, ∢: O(3)H(30)O(4) 147°.

Furthermore, we obtained the diastereomeric Schiff bases **26** from racemic, trisubstituted **22** and (*R*)-(α)-PEAM to get AHPC-based imino ligands with modified electronic properties (Scheme 3). Both (R_p,*R*)- and (S_p,*R*)-**26** were isolated in practically quantitative chemical yields after chromatographic separation (*de* > 99% by ^1H NMR analysis). As for **25** (as well as for the respective AHPC derivatives **24**[13d]), the less soluble diastereomer of **26** has the higher chromatographic mobility. The X-ray investigation of this diastereomer allowed us to assign its configuration as (S_p,*R*) (Figure 10).

It should be noted that in contrast to (*R*,S_p,*R*)-**25** in which O-H···O intramolecular H bonds are formed, in the crystal structure of (S_p,*R*)-**26** the N-H···O H bond is observed. Thus

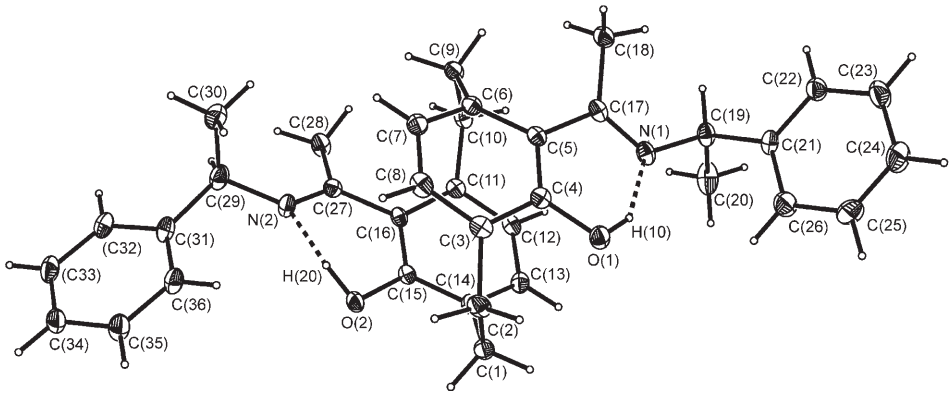


Figure 9. X-ray crystal structure of bis-imine (*R*,S_p,*R*)-**25**. Selected bond lengths [Å] in H-bonded rings: O(1)–C(4) 1.356(4), O(2)–C(15) 1.350(4), N(1)–C(17) 1.290(5), N(2)–C(27) 1.278(4), C(5)–C(17) 1.484(4), C(16)–C(27) 1.492(4), C(4)–C(5) 1.412(5), C(15)–C(16) 1.418(5). Parameters of hydrogen bonds: O(1)-H(10)···N(1) 1.73 Å, O(1)H(10)N(1) 149°, O(1)···N(1) 2.539(4) Å; O(2)-H(20)···N(2) 1.63 Å, O(2)H(20)N(2) 153°, O(2)···N(2) 2.488(4) Å.

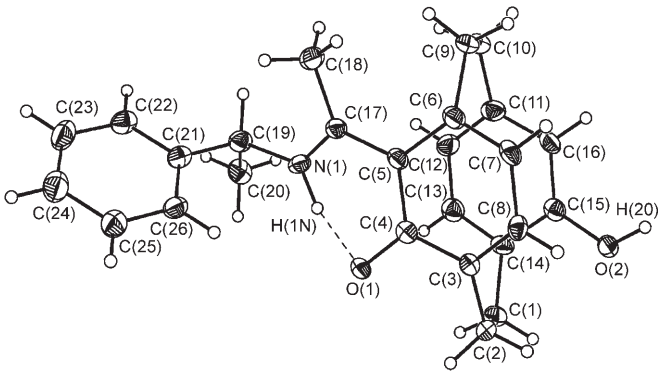
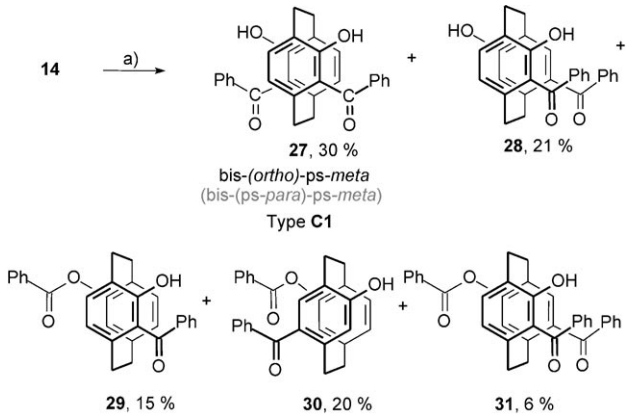


Figure 10. X-ray crystal structure of Schiff base (S_p,*R*)-**26.** Selected bond lengths [Å]: O(1)−C(4) 1.305(5), O(2) −C(15) 1.368(5), N(1) −C(17) 1.308(7), C(5) −C(17) 1.448 (6), C(4) −C(5) 1.449(7). Parameters of hydrogen bond: O(1)-H(10)···N(1) 1.56 Å, O(1)H(10)N(1) 160°, O(1)···N(1) 2.478(9).



Scheme 4. Acylation of diphenol **14** with benzoylchloride. a) 6 equiv BzCl, $TiCl_4$, CH_2Cl_2, RT.

in the latter crystal the equilibrium between two possible tautomers is shifted towards the enamine form. In addition to the position of hydrogen which was located in the vicinity of N(1) atom, the pronounced variation of the N(1)−C(17), C(17)−C(5), C(4)−C(5), C(4)−O(1) bonds (Figures 9–10), respectively, can serve as an unequivocal support of the presence of such tautomer in **26**. The stabilization of the enamine tautomer in **26** may be caused by the fact that an additional intermolecular H bond is established: O(2)−H(2O)···O(1) (y, $2-x$, $z+1/4$) (O(2)···O(1) 2.754(7) Å, H(2O)···O(1) 1.82 Å, O(2)H(2O)O(1) 164°), making the molecules assemble into a chiral helix.

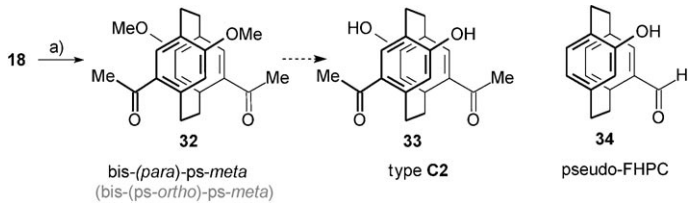
The bis-acylation technique elaborated above was next applied to the reaction of diphenol **14** with benzoylchloride, but the reaction was carried out at room temperature. In contrast to the reaction with AcCl and to the results obtained for the acylation of the monophenol **15** (leading to the single *ortho*-substituted product, namely, 5-benzoyl-4-hydroxy[2.2]paracyclophane (BHPC)),[13d] this one was neither chemo- nor regioselective, and gave rise to a number of *C*/*O*-acylated products of both *ortho*- and *para*-structure (Scheme 4). Preparative chromatography provided five fractions: the expected *ortho*-*C*-diacylated diphenol (5,16-dihydroxy[2.2]paracyclophane-4,15-diyl)bis(phenylmethanone (**27**, bis-(*ortho*)-pseudo-*meta*, type **C1**), *ortho*-*para*-diacylated 5,16-dihydroxy[2.2]paracyclophane-4,13-diyl)bis(phenyl-methanone (**28**) together with a small amount of its mono-*O*-benzoyl derivative 7,16-dibenzoyl-15-hydroxy-[2.2]paracyclophan-4-yl benzoate (**31**), and two mono-*O*/mono-*C*-acylation products namely, the respective 16-benzoyl-15-hydroxy[2.2]paracyclophan-4-yl benzoate (**29**, *ortho*-*C*) and 12-benzoyl-15-hydroxy-[2.2]paracyclophan-4-yl benzoate (**30**, *para*-*C*). The substitution pattern of **28** was confirmed by the presence of two singlets at $\delta = 5.93$ and 6.87 ppm (*para*-substituted aromatic ring) and two doublets ($^3J =$ 7.8 Hz) at 6.39 and 7.10 ppm (*ortho*-substituted aromatic ring). The structures of the more complex *O*-/*C*-acylated compounds **29** and **30** were established by a series of ^{1}H-NOESY, ^{1}H-^{13}C HMQC and HMBC correlation experiments.

In compounds **28** and **31** two benzoyl groups are placed opposite the pseudo-*gem*-position to each other, thus giving rise to the closure of the etheno bridge with formation of a rigid "orthogonal cyclophane", as it was carried out for the respective diketone pseudo-*gem*-dibenzoyl[2.2]paracyclophane under McMurry conditions followed by stilbene–phenanthrene photocyclization.[26]

The different chemo- and regioselectivity of the diacylation reactions of diphenol **14** towards acetyl- and benzoylchloride (in contrast to the exclusive *ortho*-regioselectivity of the monoacylation of monophenol **15** under the action of aromatic and aliphatic acylchlorides[13d]) reveals that in the case of more complicated bifunctional compounds, no general prediction of any clear-cut regioselectivity can be made at this time, and the reaction conditions should be adjusted properly, by applying a certain reagent if necessary, in order to achieve the selectivity desired.

***para*-Regioselective diacylation of pseudo-*meta*-dimethoxy-[2.2]paracyclophane (18)**: In pursuing our investigations further, we have also carried out the acylation of the pseudo-*meta*-dimethoxy[2.2]paracyclophane **18** with AcCl at a 1:6:6 reagent ratio for 20 h. As expected, the reaction was *para*-regioselective (as found by us for the acylation of 4-methoxy[2.2]paracyclophane[13d]) and it produced 1,1′-[7,12-dimethoxy[2.2]paracyclophane-4,15-diyl]diethanone (**32**, bis-(*para*)-pseudo-*meta*, type **C2**) as the sole product (Scheme 5). The substitution pattern of both functional units in this compound mimics that of the recently obtained 12-hydroxy[2.2]paracyclophane-4-carbaldehyde (**34**, pseudo-FHPC, of the pseudo-*ortho*-structure), a novel origin for planar chiral diol[13o] and iminophenol ligands.[36b] The synthesis of the bis-bifunctional compound **33** is also envisaged by deprotection of the hydroxy-groups of **32**.

Pseudo-*gem*-regioselective electrophilic substitution of pseudo-*meta*-bis(methoxycarbonyl[2.2]paracyclophane (20):

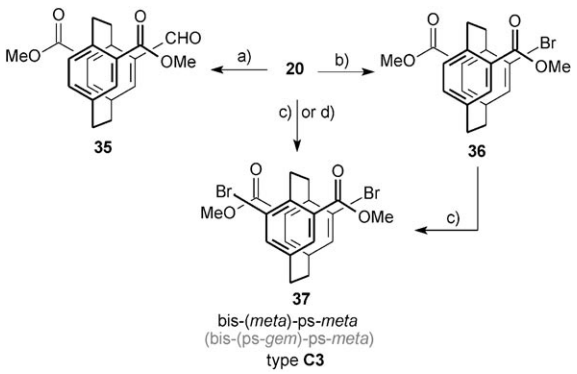


Scheme 5. *para*-Regioselective diacylation of **18**. a) 6 equiv AcCl, $TiCl_4$, CH_2Cl_2, 40 °C, 71 %.

The regioselective pseudo-*gem* bromination of 4-carboxy-[2.2]paracyclopane and its methyl ester was described by Cram and Reich already,[37a] and this approach was further used for the regioselective substitution of amide and oxazoline derivatives of this acid[19,43] or of 4-tosyl-[2.2]paracyclophane.[44] Recently the formylation of 4-methoxycarbonyl[2.2]paracyclophane was found to be efficient for the generation of the pseudo-*gem* substitution pattern.[37b] To the best of our knowledge, the only example of a double pseudo-*gem*-regioselective substitution, namely, the chloromethylation of *para*-bis(methoxycarbonyl)-[2.2]paracyclophane was reported to produce the respective tetrasubstituted derivative.[16] We have undertaken the investigation of the reactivity and regioselectivity of pseudo-*meta*-bis(methoxycarbonyl)[2.2]paracyclophane (**20**) in double pseudo-*geminal* substitution reactions.

The formylation of **20** with Cl_2CHOCH_3 (2.4 equiv) in the presence of $TiCl_4$ (4 equiv) in dichloromethane at room temperature was extremely slow and in 13 days went halfway to completion only. Under these conditions only monoformylation was achieved (^{1}H NMR control), even with the set of the reagents being added three times. However, the process was highly pseudo-*gem*-regioselective, and dimethyl 8-formyl[2.2]paracyclophane-4,15-dicarboxylate (**35**) was isolated from the reaction mixture in 49 % chemical yield (Scheme 6); unreacted **20** was recovered in 40 % yield.

Next, the Fe-catalyzed, room temperature bromination of the diester **20** was investigated (Scheme 6). In contrast to



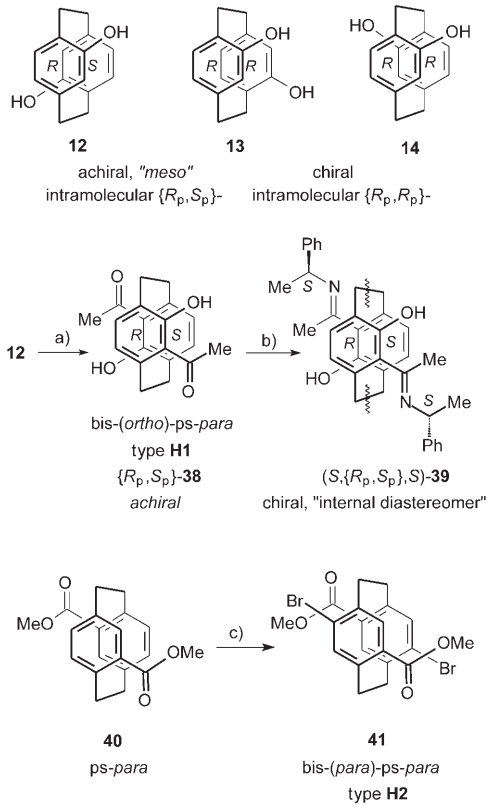
Scheme 6. Pseudo-*gem*-regioselective electrophilic mono- and disubstitution of **20**. a) 6 equiv $Cl_2CH_2OCH_3$, $TiCl_4$, 49 %; b) 2 equiv Br_2, Fe, RT, 3 d, 80 %; c) 10 equiv Br_2, Fe, RT, 10 d, 93 %; d) 20 equiv Br_2, Fe, T = 42 °C, 10 h, 88 %.

the formylation, in the bromination reaction with 2.4 mol equiv of Br_2 at room temperature the starting compound was consumed by 80 % (^{1}H NMR control) already in three days. This reaction also gave the product of the pseudo-*gem*-regioselective monosubstitution, dimethyl 8-bromo-[2.2]paracyclophane-4,15-dicarboxylate (**36**), which was completely separated from starting material **20** by chromatography. The next bromination experiment was carried out in a similar manner, but after three days a huge excess of the reagents (up to 10 mol equiv of Br_2 in total) was added and the mixture was stirred for a further 10 day-period. ^{1}H NMR spectra showed full consumption of **20** and pseudo-*geminal* regioselective formation of the target dimethyl 8,13-dibromo[2.2]paracyclophane-4,15-dicarboxylate (**37**, bis-(*meta*)-pseudo-*meta*, type **C3**). The dibromination was accelerated by refluxing **20** with 20 mol equiv of Br_2 in a 2:1 CH_2Cl_2/CCl_4 solvent system. The reaction was complete in 10 h, and the dibromide **37** was isolated by preparative chromatography in 88 % yield. We believe this compound to be a promising precursor of a wide range of novel [2.2]paracyclophane derivatives obtainable by further chemical transformations of its bromine atoms and/or of its ester groups.

***ortho-* and pseudo-*gem*-Regioselective double electrophilic substitution of achiral pseudo-*para*-disubstituted [2.2]paracyclophanes 12 and 40**: To expand the scope of the double electrophilic substitution onto the synthesis of achiral bis-bifunctional compounds, we have applied the above diacylation and dibromination techniques to the achiral 4,16-dihydroxy[2.2]paracyclophane (**12**) and to 4,16-bis(methoxycarbonyl)[2.2]paracyclophane (**40**)[10a] (of the pseudo-*para*-structure). As expected, both reactions retained the regioselectivities which are characteristic for their pseudo-*meta* regioisomers and produced the respective 1,1′-[5,15-dihydroxy[2.2]paracyclophane-4,16-diyl]diethanone (**38**, bis-(*ortho*)-pseudo-*para*, type **H1**) and dimethyl 7,13-dibromo[2.2]paracyclophane-4,16-dicarboxylate (**41**, bis-(*para*)-pseudo-*para*, type **H2**, Scheme 7).

Here, we would like to touch upon some points of a specifically stereochemical interest. Ernst and Wittkowski have proposed to consider disubstituted [2.2]paracyclophane derivatives with *identical* groups in both aromatic rings not only as regio- but also as stereoisomers.[45] In such compounds there are two constitutionally equal planes of chirality, passing through the planes of both aromatic rings, and optical activity depends on the sense of chirality of these two elements. That is the reason why, for example, biphenols **13** and **14** (with *R* stereochemical descriptors for both aromatic rings, $\{R_p,R_p\}$[46]) may be regarded as internal (intramolecular) "chiral diastereomers", whereas biphenol **12** is described as $\{R_p,S_p\}$, and so is an internal achiral "*meso*-compound" (Scheme 7). The same statements are true for all compounds of chiral (**A**–**C**) and achiral patterns (**E**–**H**) as well as for the respective symmetrical tetrasubstituted [2.2]paracyclophanes derived from them.

However, the reaction of achiral **38** with two equivalents of (*S*)-(α)-PEAM furnishes an interesting Schiff base



Scheme 7.

$(S,\{R_p,S_p\},S)$-**39** (or (S_c,S_c)-**39**) which formally has four chiral elements and is, in this case, chiral due to the chirality of its asymmetric centers (Scheme 7). If one considers independently both functional units of this compound ((R_p,S)-, top ring, and (S_p,S)-, bottom ring), then their similarity to the functional fragments of diastereomers of the imino-type ligands derived from AHPC and (*S*)-(α)-PEAM, namely (R_p,S)- and (S_p,S)-**24** becomes clear. So $(S,\{R_p,S_p\},S)$-**39** could be regarded as "internal diastereomer". Both ^{1}H and ^{13}C NMR spectra are an excellent illustration of this phenomenon. The spectra, containing two characteristic sets of signals of equivalent intensity, appear to be those of the equimolar diastereomeric mixture. Obviously, the individual diastereomeric fragments could not have been separated chemically in this case.

The other stereochemical analogy of this phenomenon may be found among [2.2]paracyclophane derived salen ligands **42**, described and classified (in accordance with their structural and configurational symmetry) by us recently.[13j,47] These ligands also have four chiral elements (two independent planar chiral paracyclophane moieties and two chiral centers), and in the case when they are structurally symmetrical, but two paracyclophanyl fragments have opposite configurations (*R* and *S*), they also became chiral due to the chirality of the diamine fragment only ((S_p,R,R,R_p)-**42**, Figure 11, left). At the same time, diastereomeric bis-bifunctional iminoligands (R,S_p,R)- and (R,R_p,R)-**25** (Scheme 3, which formally may be considered as $(R,\{S_p,S_p\},R)$- and

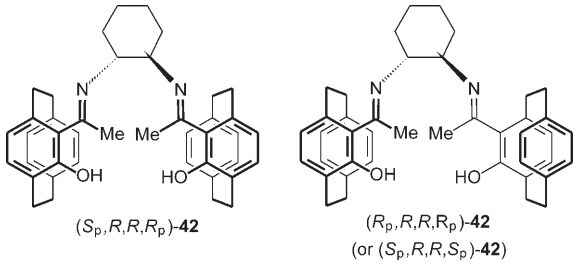


Figure 11. Intramolecular stereochemical analogues for bis-iminoligands **25** and **38**.

$(R,\{R_p,R_p\},R)$-**25**), may be compared with structurally and stereochemically symmetrical salens such as ((S_p,R,R,S_p)-**42** or (R_p,R,R,R_p)-**42**, Figure 11, right).

Enantioselective diethylzinc addition to benzaldehyde

To estimate the ability of the newly synthesized imino ligands to function as chiral inductors in asymmetric catalysis, we have carried out the model reaction of diethylzinc addition to benzaldehyde (Table 2).

Thus, for the diastereomeric ligands **25** a matched-mismatched effect was observed (Table 2, entries 1, 2), and (R,S_p,R)-**25** showed a catalytic activity very close to that shown by the respective structurally similar (R_p,S)-AHPC analog (cf. 76% (*R*) against 82% (*S*),[42] Table 2, entry 3). The ligand (S_p,R)-**26** (with additional hydroxy group), in contrast, influenced the reaction in the opposite direction providing (*S*)-1-phenylpropanol with good selectivity (Table 2, entry 4). The "internal diastereomer" **39** showed some (though very negligible) catalytic activity with the result lying between that obtained for the two diastereomers of the respective imino-ligands **25** (Table 2, entry 5).

Prospects

Synthesis: Our experience[20] and the literature data[16–19] reveal that *ortho*-, *para*-, and pseudo-*gem*-regioselective double electrophilic substitution of symmetrical chiral and achiral disubstituted [2.2]paracyclophanes constitute a general and useful approach to the synthesis of the different types of tetrasubstituted derivatives. The combination of symmetrical disubstituted origins with different substitution patterns, certain substituents (chosen in accordance with the known regularities of the regioselective electrophilic substitution of cyclophanes), and appropriate reactions (bromination, acylation, formylation, oxaloylation, nitration, sulfonation etc.) are a good way to synthesize the majority of the 28 possible symmetrical regioisomeric tetrasubstituted [2.2]paracyclophanes. Moreover, the direct lithiation/electrophilic exchange—a useful method for the regioselective functionalization of either aromatic rings or ethano bridges[48–50] of [2.2]paracyclophanes bearing DMG substituents (DMG = direct metallation groups: phenols- and car-

boxylic acids derivatives, sulfoxides etc.[51])—looks promising to be extended to the functionalization of disubstituted paracyclophanes, which, to the best of our knowledge, has never been investigated.

The possibility to carry out mono-electrophilic substitution makes trisubstituted [2.2]paracyclophanes available for further conversions, as modifiers for well known ligands[18] or bidentate ligands whose extra substituent may be used for fixation on a solid support.[17]

Further development may also include an unsymmetric double electrophilic substitution of disubstituted [2.2]paracyclophanes and/or a stepwise condensation of carbonyl components with configurationally opposite amines, which could lead to a variety of structurally and configurationally unsymmetric bis-bifunctional ligands.

The synthesis of Schiff bases of bis-carbonyl compounds with various diamines (for example, bis-(*ortho*)-pseudo-*meta* **21** with ethylendiamine) is in progress now.

Applications: For a long period of time the investigation of the chemistry of tetrasubstituted cyclophanes has been restricted to theoretical studies of "through space" donor–acceptor π–π interactions.[8,9] Only recently charge transfer effects were successfully applied by Bazan et al. in materials chemistry for the construction of nonlinearoptic and optoelectric materials from several especially designed tetrasubstituted compounds.[3]

A more detailed insight into the structures of the bis-bifunctional [2.2]paracyclophanes reveals priorities of their potential usefulness. It is clear from Figure 5, that all chiral C_2-symmetric structures look attractive as prospective chiral ligands for asymmetric catalysis. Thus the functional groups in the regioisomers **A1**–**A3**, **B1** and **C1**–**C3** form two *identical* (chemically and stereochemically) systems {X–Y} both of which mimic one of the typical disubstituted chiral ligand patterns based on [2.2]paracyclophane[7] (*ortho*-, pseudo-*ortho*-, and pseudo-*gem*-) and may independently work as chiral promoters. The structures **B2** and **B3**, in contrast, have two *different* {X–X} and {Y–Y} functional systems of pseudo-*ortho*-architecture, whereas structure **D** consists of two pseudo-*ortho*-systems with identical substituents {X–X}. Note also that the second pair of substituents may affect the electronic properties of the ligand. Furthermore, all symmetrical tetrasubstituted compounds have a great potential to be used not only as chiral ligands for asymmetric catalysis, but also as a useful platform for the composition of liquid crystalline or NLO materials, monomers for polymer synthesis, objects for biological research *etc*. We hope that the elaboration of useful and versatile methods for their synthesis will promote the development in the titled areas.

Conclusion

We have for the first time investigated the reactivity and the regioselectivity of electrophilic substitution of chiral pseudo-*meta*- and achiral pseudo-*para*-disubstituted [2.2]paracyclophanes. We have developed conditions for chemoselective disubstitution and established that these reactions can occur *ortho*-, *para*- or pseudo-*gem*-regioselectively, providing for an efficient synthesis of chiral and achiral bis-bifunctional tetrasubstituted [2.2]paracyclophanes. The approach worked out here may be considered as a powerful tool for the preparation of the title compounds with diverse substitution patterns and 3D-structures. We have determined the possible number of chiral and achiral patterns (10 and 18, respectively), described their symmetry properties, and introduced a straightforward descriptor system (based on customary *ortho*-, *meta*-, *para*-, and "pseudo"-prefixes accepted in [2.2]paracyclophane chemistry), allowing an unambiguous designation of all these patterns. Preliminary results of the application of several bis-bifunctional imino-type ligands in asymmetric catalysis have also been presented. Further investigations in this area are underway, including:

1) Application of the regioselective double electrophilic substitution outlined above to novel pseudo-*meta*- and pseudo-*para*-disubstituted substrates (dicarboxylic acid derivatives, sulfoxides, etc.), and to chiral *para*-disubstituted [2.2]paracyclophanes;
2) extension of the range of electrophilic reactions (formylation, oxaloylation, nitration, etc.);
3) examination of the reactivity (mono-/disubstitution) and regioselectivity (*ortho*-/lateral) of the lithiation/electrophile exchange of symmetrical DMG-disubstituted [2.2]paracyclophanes.

Experimental Section

General remarks: ^{1}H and ^{13}C NMR: Bruker AMX-400 at 400.13 and 100.61 MHz, respectively, in $CDCl_3$ and [D_6]DMSO. Residual signals of the solvent protons with the chemical shifts $\delta = 7.27$ ($CDCl_3$) and 2.5 ppm ([D_6]DMSO) were used as internal standards. MS: Kratos MS 90 mass spectrometer (70 eV) at 200 or 250 °C. TLC: Sorbfil UV-254 plates (CTX-1 A); chromatographic purification and separation of isomers were carried out using Kieselgel 60 silica gel (Merck). Optical rotations: EPO-1 and Perkin Elmer in thermostated cell (25 °C). Et_2Zn (1.1 M solution in toluene) was purchased from Aldrich and used without purification. All asymmetric additions of diethylzinc to aldehydes were carried out in dry glassware under argon in accordance with the standard procedure.[12j]

Uncatalyzed bromination of [2.2]paracyclophane (1): To a suspension of **1** (21.55 g, 0.104 mmol) in CCl_4 (300 mL) with vigorous stirring and heating (55 °C) was added dropwise a solution of Br_2 (99.45 g, 0.62 mmol) in CCl_4 (30 mL), and the resulting mixture was stirred for 2 h (TLC control). Excess bromine and solvent were evaporated under reduced pressure, and the residue was washed with warm hexane (45–55 °C, 75 mL) and Et_2O (75 mL) to remove possible polybrominated byproducts. The mixture of dibromides **9** and **10** was washed with $CHCl_3$ (2×135 mL) and the remaining solid was recrystallized twice from dioxan to afford pseudo-*para*-dibromide **10** (12.88 g, 34 %). M.p. 250–251 °C; lit. m.p. 248.5–250 °C.[11a] The chloroform solution was evaporated and analytically pure pseudo-*meta*-dibromide **9** (16.29 g, 43 %) was isolated as a result of fractional recrystallization of the solid from ethanol; m.p. 125–125.5 °C; lit. m.p. 123.5–125.5 °C.[11a]

4-Bromo[2.2]paracyclophane-15-ol (16): To a solution of **9** (1.00 g, 2.73 mmol) in Et_2O (20 mL) *n*BuLi (1 mL of 3.27 N solution in hexane,

3.27 mmol) was added dropwise at room temperature, and the resulting suspension was stirred for 3 h. Then $B(OMe)_3$ (0.7 mL, 5.90 mmol) was added and the mixture was stirred overnight at room temperature. A solution of NaOH (2 g in 10 mL of H_2O, 50 mmol) and 30% H_2O_2 (6.5 mL) were added, and the reaction mixture was stirred for 1 h. The organic phase was separated and the aqueous phase was extracted with Et_2O (3× 100 mL). The combined organic phases were dried with Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was separated by preparative chromatography on silica gel with CH_2Cl_2 to afford **16** (0.71 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.79–3.07 (m, 6H, bridge-CH_2-), 3.08–3.26 (m, 1H, bridge-CH_2-), 3.27–3.43 (m, 1H, bridge-CH_2-), 4.45 (s, 1H, OH), 5.64 (s, 1H, 5-H), 6.22, 6.47 (br d, ^3J = 7.8 Hz, 2H, 7-, 12-H or 8-, 13-H), 6.57 (s, 1H, 16-H), 7.01, 7.10 ppm (2d, ^3J = 7.8 Hz, 2H, 8-, 13-H or 7-, 12-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.77, 30.05, 30.37, 30.63 (C-1, -2, -9, -10), 117.70, 120.51, 125.59, 126.68, 126.79, 132.48 (C-5, -7, -8, -12, -13, -16), 120.94, 123.56, 135.28, 136.73 (C-6, -3, -11, -14), 137.49, 150.28 ppm (C-4, -15); MS (70 eV): *m*/*z* (%): 304 $[M]^+$ (67), 302 (68) $[M]^+$, 224 $[M-Br]^+$ (13), 223 (20), 200 (11), 184 (36), 120 (100).

4-Bromo[2.2]paracyclophan-15-yl methyl ether (17): To a solution of **16** (0.50 g, 1.65 mmol) in DMF (2 mL) NaH (60% in oil, 0.072 g, 1.79 mmol) was added, the resulting brown solution was stirred at room temperature for 1 h and then MeI (0.5 mL, 8.03 mmol) was added. The reaction mixture was stirred for additional 2 h, diluted with H_2O (10 mL), extracted with Et_2O (5×20 mL), and dried with Na_2SO_4. The solvent was evaporated at reduced pressure and the solid residue was purified by preparative chromatography on silica gel with CH_2Cl_2 to furnish **17**. Recrystallization from hexane yielded analytically pure **17** (0.46 g, 87%). M.p. 113.5–114.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.82–3.05 (m, 6H, bridge-CH_2-), 3.20–3.36 (m, 2H, bridge-CH_2-), 3.71 (s, 3H, CH_3), 5.75 (d, ^4J = 1.8 Hz, 1H, 16-H), 6.23 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1H, 12-H), 6.46 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1H, 7-H), 6.53 (d, ^4J = 1.8 Hz, 1H, 5-H), 6.75 (d, ^3J = 7.8 Hz, 1H, 8-H), 7.12 ppm (d, ^3J = 7.8 Hz, 1H, 13-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.16, 34.25, 34.40, 35.10 (C-1, -2, -9, -10), 54.22 (CH_3), 115.88 (C-16), 123.84 (C-12), 126.71, 127.48, 129.81, 130.26 (C-7, -13), 136.68 (C-5), 139.86, 140.57, 141.42, 158.11 ppm (C-3, -6, -11, -14); MS (70 eV): *m*/*z* (%): 318 (30) $[M]^+$, 316 (32) $[M]^+$, 189 (11), 184 (23), 182 (25), 135 (52), 134 (100), 115 (19), 105 (41), 104 (92), 103 (90), 102 (34); elemental analysis calcd (%) for $C_{17}H_{17}BrO$: C 64.37, H 5.40, Br 25.19; found: C 64.18, H 5.36, Br 25.13.

[2.2]Paracyclophane-4,15-diol (pseudo-*meta*, 14): **From 4,15-dibromo-[2.2]paracyclophane (pseudo-*meta*, 9)**: To a solution of **9** (1.00 g, 2.73 mmol) in Et_2O (100 mL), *n*BuLi (2 mL of 3.27 N solution in hexane, 6.54 mmol) was added dropwise at room temperature; the resulting suspension was stirred for 3 h at room temperature and cooled to −78 °C. A solution of $PhNO_2$ (0.8 mL, 7.84 mmol) in Et_2O (20 mL) was added, and the reaction mixture was stirred for 5 h at −78 °C. Methanol (10 mL) and 2 M HCl (40 mL) were added, the mixture was stirred for 1 h and left overnight to warm up. The organic phase was separated and washed with H_2O (3×100 mL); the aqueous phase was extracted with Et_2O (3× 100 mL), and the combined organic phase was dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by preparative chromatography on silica gel (CH_2Cl_2) to afford **14** (0.20 g, 30%).

From 4-bromo[2.2]paracyclophane-15-ol (16): To a solution of **16** (0.50 g, 1.65 mmol) in Et_2O (100 mL), *n*BuLi (1.1 mL, 3.27 N solution in hexane, 3.63 mmol) was added dropwise at room temperature, and the resulting suspension was stirred for 3 h. The reaction mixture was treated with $B(OMe)_3$ (0.92 mL, 9.08 mol) and stirred overnight. Then NaOH solution (1 g in 5 mL of H_2O, 0.03 mol) and 30% H_2O_2 (3.5 mL) were added, and the mixture was stirred for 1 h. The organic phase was separated, the aqueous phase was extracted with Et_2O (3×100 mL) and the combined organic phases were dried with Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified on a silica gel column (CH_2Cl_2) to afford **14** (0.35 g, 87%). Analytically pure **14** was obtained by recrystallization from hexane/toluene 1:1. Decomp. temp. 200–230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77–2.96 (m, 6H, bridge-CH_2-), 3.13–2.26 (m, 2H, bridge-CH_2-), 4.42 (s, 2H, 2 OH), 5.57 (s, 2H, 5-, 8-H), 6.21 (br d, ^3J = 7.8 Hz, 2H, 7-, 12-H), 6.91 ppm (d, ^3J = 7.8 Hz, 2H, 8-, 13-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.45, 30.45 (C-1, -2, -9, -10), 117.07, 120.31, 126.10 (C-5, -7, -8, -12, -13, -16), 121.52, 137.22 (C-6, -3, -11, -14), 150.02 ppm (C-4, -15); MS (70 eV): *m*/*z* (%): 241 (26) $[M]^+$, 240 (60) $[M]^+$, 239 (13), 121 $[M-119]^+$ (52), 91 (100); elemental analysis calcd (%) for $C_{16}H_{16}O_2$: C 79.97, H 6.71; found: C 79.97, H 6.71.

***ortho*-Regioselective diacylation of [2.2]paracyclophane-4,15-diol (pseudo-*meta*-, 14) with acetyl chloride**: To a solution of **14** (0.20 g, 0.84 mmol) in CH_2Cl_2 (30 mL) $TiCl_4$ (0.55 mL, 5.04 mmol) was added at 0 °C, and the reaction mixture was allowed to warm to RT. The resulting brownish-red solution was stirred for 1 h, then acetyl chloride (0.36 mL, 5.04 mmol) was added and the mixture was stirred at 40 °C for 10 h. The reaction mixture was cooled to RT, the second portions of $TiCl_4$ (0.55 mL, 5.04 mmol) and acetyl chloride (0.36 mL, 5.04 mmol) were added successively, and the mixture was stirred at 40 °C for an additional 10 h. The reaction mixture was diluted with H_2O (10 mL) and vigorously stirred for 15 min. The organic layer was separated, washed with H_2O (2×10 mL) and dried with Na_2SO_4. The crude product was obtained after removal of the solvent in vacuo and purified by preparative chromatography on silica gel (CH_2Cl_2) to yield **21** (0.35 g, 93%).

1,1′-[5,16-Dihydroxy[2.2]paracyclophane-4,15-diyl]diethanone (bis-(*ortho*)-pseudo-*meta*-, 21): M.p. 166.5–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59 (s, 6H, 2 CH_3), 2.61–2.66 (m, 2H, bridge-CH_2-), 2.72–2.83 (m, 2H, bridge-CH_2-), 3.22–3.33 (m, 2H, bridge-CH_2-), 3.66–3.78 (m, 2H, bridge-CH_2-), 6.09 (d, ^3J = 7.8 Hz, 2H, 7-, 12-H or 8-, 13-H), 7.02 (d, ^3J = 7.8 Hz, 2H, 7-, 12-H or 8-, 13-H), 12.72 ppm (s, 2H, 2 OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.64, 26.64, 34.00, 117.45, 121.95, 125.93, 129.90, 135.95, 158.60, 200.45 ppm; MS (70 eV): *m*/*z* (%): 324 (81) $[M]^+$, 306 (6), 288 (11), 164 (13), 163 (53), 162 (100), 161 (100); elemental analysis calcd (%) for $C_{20}H_{20}O_4$: C 74.06, H 6.21; found: C 74.03, H 6.18.

Acylation of **14** under the conditions described in Table 2 (entries 1–4) leads to mixtures of **21**, **22** and **23**. Combined reaction mixtures from these experiments were separated by preparative chromatography on silica gel (CH_2Cl_2/Et_2O 10:1) to produce the individual derivatives **21**, **22** and **23**.

1-[5,16-Dihydroxy[2.2]paracyclophan-4-yl]ethanone (22): M.p. 131.5–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59 (s, 3H, CH_3), 2.60–2.77 (m, 2H, bridge-CH_2-), 2.82–2.94 (m, 2H, bridge-CH_2-), 3.06–3.22 (m, 2H, bridge-CH_2-), 3.24–3.34 (m, 1H, bridge-CH_2-), 3.61–3.72 (m, 1H, bridge-CH_2-), 4.63 (s, 1H, C-15(OH)), 5.64 (d, ^4J = 1.8 Hz, 1H, 16-H), 6.05 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1H, 12–12), 6.27 (d, ^3J = 7.8 Hz, 1H, 7- or 8-H), 6.87 (d, ^3J = 7.8 Hz, 1H, 7- or 8-H), 7.07 (d, ^3J = 7.8 Hz, 1H, 13-H), 12.82 ppm (s, 1H, C-4(OH)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.89, 24.99, 26.85, 30.49, 33.22, 115.49, 118.08, 120.02, 122.00, 122.71, 125.11, 125.51, 130.39, 135.78, 137.85, 150.04, 158.67, 200.62 ppm; MS (70 eV): *m*/*z* (%): 283 (21) $[M]^+$, 282 (79) $[M]^+$, 163 (27), 162 (92), 147 (19), 134 (20), 121 (41), 120 (100), 115 (13); elemental analysis calcd (%) for $C_{18}H_{18}O_3$: C 76.57, H 6.43; found: C 76.41, H 6.42.

16-Acetyl-15-hydroxy[2.2]paracyclophan-4-yl acetate (23): M.p. 143–143.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.60–2.74 (m, 2H, bridge-CH_2-), 2.85–3.06 (m, 3H, bridge-CH_2-), 3.11–3.21 (m, 1H, bridge-CH_2-), 3.26–3.35 (m, 1H, bridge-CH_2-), 3.61–3.71 (m, 1H, bridge-CH_2-), 6.11 (d, ^4J = 1.8 Hz, 1H, 5-H), 6.25–6.33 (m, 2H, 7-, 15- or 16-H), 6.70, 6.97 (2d, ^3J = 7.8 Hz, 2H, 8-, 15- or 16-H), 12.78 ppm (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.18, 25.29, 25.81, 26.91, 30.55, 33.04, 118.36, 121.56, 122.80, 124.87, 125.03, 125.49, 127.78, 131.85, 135.50, 138.05, 145.38, 158.65, 164.50, 200.44 ppm; MS (70 eV): *m*/*z* (%): 324 (38) $[M]^+$, 282 (15), 264 (10), 163 (21), 161 (94), 147 (16), 134 (18), 133 (17), 115 (16), 120 (100); elemental analysis calcd (%) for $C_{20}H_{20}O_4$: C 74.06, H 6.21; found: C 74.20, H 6.24.

Acylation of [2.2]paracyclophane-4,15-diol (pseudo-*meta*-, 14) with benzoyl chloride: The reaction was carried out as described for acetyl chloride by double successive addition of the respective reactants, $TiCl_4$ (1.24 mL, 11.25 mmol) and benzoyl chloride (1.31 mL, 11.25 mmol) to **14** (0.045 g, 1.88 mmol); the reaction mixture was, however, stirred for 10 h at room temperature rather than refluxed in CH_2Cl_2. The reaction mixture was diluted with H_2O (50 mL) and vigorously stirred for 15 min. The organic layer was separated, washed with H_2O (2×60 mL), dried with

Na_2SO_4 and the solvent was evaporated in vacuo to produce a mixture of **27–31**. The products were separated by preparative chromatography on silica gel ($CHCl_3$ (**28**, **30**), CH_2Cl_2/Et_2O 10:1 (**27**) and cyclohexane/Et_2O 10:1 (**29**, **31**)).

(5,16-Dihydroxy[2.2]paracyclophane-4,15-diyl)bis(phenylmethanone) (bis-(*ortho*)-pseudo-*meta*-, 27): Isolated yield: 0.256 g (30%); m.p. 188–189°C; H NMR (600 MHz, $CDCl_3$): δ = 1.77–1.99 (m, 2H, bridge-CH_2-), 2.14–2.31 (m, 2H, bridge-CH_2-), 2.80–2.96 (m, 2H, bridge-CH_2-), 3.29–3.44 (m, 2H, bridge-CH_2-), 6.27 (d, ^3J = 7.8 Hz, 2H, 7- and 12-H or 8- and 13-H), 7.23 (d, ^3J = 7.8 Hz, 2H, 8- and 13-H or 7- and 12-H), 7.38 (t, ^3J = 7.8 HZ, 4H, 4 *meta*-arom.), 7.50 (dt, ^3J = 7.8 Hz, 2H, 2 *para*-arom.), 7.65 ppm (dd, ^3J = 7.8, ^4J = 1.8 Hz, 4H, 4 *ortho*-arom.), 11.90 ppm (s, 2H, C-5(OH), C-16(OH)); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 28.61, 37.24, 119.78, 125.22, 128.36, 128.95, 129.19, 132.44, 134.62, 140.16, 142.05, 162.44, 200.62 ppm; MS (70 eV): *m*/*z* (%): 449 (13) $[M]^+$, 448 (45) $[M]^+$, 447 (52) $[M]^+$, 430 (23), 412 (18), 238 (20), 237 (46), 226 (15), 225 (62), 224 (82), 223 (100), 222 (17), 212 (25), 211 (22), 210 (16), 209 (54), 208 (19), 207 (16), 206 (13), 182 (12), 181 (56), 179 (18), 178 (40), 177 (24), 176 (25), 167 (29), 166 (22), 165 (51), 147 (27), 146 (11), 128 (12), 120 (50), 119 (15), 115 (14), 105 (67), 104 (35), 103 (10); elemental analysis calcd (%) for $C_{30}H_{24}O_4$: C 80.34, H 5.39; found: C 80.47, H 5.34.

(5,16-Dihydroxy[2.2]paracyclophane-4,13-diyl)bis(phenylmethanone) (28): Isolated yield: 0.177 g (21%); decomp. temp. < 300°C; ^{1}H NMR (600 MHz, DMSO): δ = 2.56–2.82 (m, 4H, bridge-CH_2-), 2.83–2.97 (m, 1H, bridge-CH_2-), 2.99–3.12 (m, 1H, bridge-CH_2-), 3.27–3.43 (m, 2H, bridge-CH_2-), 5.93 (s, 1H, 16-H), 6.39 (d, ^3J = 7.8 Hz, 1H, 7- or 8-H), 6.87 (s, 1H, 13-H), 7.10 (d, ^3J = 7.8 Hz, 1H, 8- or 7-H), 7.41–7.80 (m, 10H, 2 Ph), 9.92 (s, 1H, C-16(OH)), 11.68 ppm (s, 1H, C-5(OH)); ^{13}C NMR (151 MHz, DMSO): δ = 29.55, 30.07, 35.94, 36.45, 120.72, 124.91, 125.64, 126.66, 127.70, 128.62, 129.14, 129.47, 130.51, 130.61, 132.54, 133.43, 135.78, 136.78, 141.32, 141.98, 145.32, 145.61, 161.28, 162.27, 195.95, 200.54 ppm; MS (70 eV): *m*/*z* (%): 449 (12) $[M]^+$, 448 (40) $[M]^+$, 447 (47) $[M]^+$, 430 (18), 419 (13), 237 (12), 226 (13), 224 (92), 223 (100), 211 (15), 209 (21), 207 (10), 196 (14), 195 (41), 181 (36), 178 (16), 177 (10), 167 (14), 166 (12), 165 (27), 153 (12), 152 (24), 147 (10), 105 (66); elemental analysis calcd (%) for $C_{30}H_{24}O_4$: C 80.34, H 5.39; found: C 80.08, H 5.30.

16-Benzoyl-15-hydroxy[2.2]paracyclophan-4-yl benzoate (29): Isolated yield: 0.130 g (15%); m.p. 152°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.37 (m, 1H, 10a-H), 2.41 (m, 1H, 9b-H), 2.58 (m, 1H, 10b-H), 2.76 (m, 1H, 2a-H), 2.85 (m, 1H, 9a-H), 3.00 (m, 1H, 1b-H), 3.19 (m, 1H, 1a-H), 3.41 (m, 1H, 2b-H), 6.27 (d, ^4J = 1.8 Hz, 1H, 5-H), 6.40 (d, ^3J = 7.8 Hz, 1H, 13-H), 6.48 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1H, 7-H), 7.17 (d, ^3J = 7.8 Hz, 1H, 12-H), 7.19 (d, ^3J = 7.8 Hz, 1H, 8-H), 7.77 (d, ^3J = 7.5 Hz, 2H, 2 *ortho*-H, PhC(O)-), 7.51 (brt, ^3J = 7.5 Hz, 2H, 2 *meta*-PhC(O)-), 7.62 (m, 3H, *para*-PhC(O)-, 2 *meta*-PhOC(O)-), 7.72 (t, ^3J = 7.5 Hz, 1H, *para*-PhOC(O)-), 8.28 (d, ^3J = 7.5 Hz, 2H, *ortho*- PhOC(O)-), 11.86 ppm (s, 1H, OH); ^{13}C NMR (151 MHz, DMSO): δ = 25.80, 26.04, 30.44, 32.51, 121.92, 122.35, 124.51, 124.59, 124.60, 124.78, 125.30, 125.62, 125.95, 127.60, 128.57, 128.60, 129.64, 132.52, 135.88, 136.39, 139.84, 145.38, 158.14, 160.26, 196.13, 196.32 ppm; MS (70 eV): *m*/*z* (%): 449 (22) $[M]^+$, 448 (53) $[M]^+$, 430 (16), 325 (11), 225 (18), 224 (69), 223 (87), 222 (13), 209 (15), 195 (14), 181 (14), 165 (17), 152 (14), 120 (10), 106 (43), 105 (100); elemental analysis calcd (%) for $C_{30}H_{24}O_4$: C 80.34, H 5.39; found: C 80.48, H 5.26.

12-Benzoyl-15-hydroxy[2.2]paracyclophan-4-yl benzoate (30): Isolated yield: 0.172 g (20%); decomp. temp. 225–230°C; ^{1}H NMR (600 MHz, DMSO): δ = 2.36–2.72 (m, 2H, bridge-CH_2-), 2.73–2.87 (m, 2H, bridge-CH_2-), 2.98–3.10 (m, 1H, bridge-CH_2-), 3.11–3.21 (m, 1H, bridge-CH_2-), 3.42–3.54 (m, 2H, bridge-CH_2-), 5.82 (s, 1H, 16-H), 6.20 (d, ^4J = 1.8 Hz, 1H, 5-H), 6.56 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1H, 7-H), 7.02 (d, ^3J = 7.8 Hz, 1H, 8-H), 7.03 (s, 1H, 13-H), 7.40–7.52 (m, 4H, *meta*-Ph), 7.58 (brd, ^3J = 7.5 Hz, 2H, 2 *ortho*-H, Ph), 7.61 (t, ^3J = 7.5 Hz, 1H, *para*-Ph), 7.71 (t, ^3J = 7.5 Hz, 1H, *para*-Ph), 7.89 (d, ^3J = 7.5 Hz, 2H, *ortho*-Ph), 10.07 ppm (s, 1H, OH); ^{13}C NMR (151 MHz, DMSO): δ = 30.62, 30.68, 34.74, 35.31, 124.74, 124.84, 125.29, 125.34, 125.75, 129.42, 130.06, 130.17, 130.58, 131.67, 132.37, 132.79, 135.17, 137.22, 141.13, 142.61, 145.86, 150.16, 161.17, 164.54, 196.86, 215.18 ppm; MS (70 eV): *m*/*z* (%): 449 (39) $[M]^+$, 448 (66) $[M]^+$, 343 (11), 328 (13), 225 (25), 224 (74), 223 (46), 195 (16), 181 (20), 165 (18), 152 (15), 120 (10), 106 (35), 105 (100); elemental analysis calcd (%) for $C_{30}H_{24}O_4$: C 80.34, H 5.39; found: C 80.08, H 5.26.

7,16-Dibenzoyl-15-hydroxy[2.2]paracyclophan-4-yl benzoate (31): Isolated yield: 0.066 g (6%); m.p. 238.5–239°C; ^{1}H NMR (600 MHz, DMSO): δ = 2.65–3.35 (m, 8H, bridge-CH_2-), 6.61 (d, ^3J = 7.8 Hz, 1H, 12- or 13-H), 6.69 (s, 1H, 5- or 8-H), 7.17 (s, 1H, 8- or 5-H), 7.33 (d, ^3J = 7.8 Hz, 1H, 13- or 12-H), 7.55–7.95 (m, 13H, 3 Ph), 8.35 (d, ^3J = 7.5 Hz, 2H, *ortho*-Ph), 11.72 ppm (s, 1H, OH); ^{13}C NMR (151 MHz, DMSO): δ = 29.75, 29.84, 35.00, 35.70, 119.98, 126.11, 127.43, 128.82, 128.90, 129.01, 129.79, 129.83, 130.10, 130.41, 130.52, 131.45, 132.13, 132.80, 133.01, 133.71, 134.88, 137.49, 139.19, 140.95, 143.96, 145.24, 152.52, 160.72, 161.04, 163.96, 195.29, 199.69 ppm; MS (70 eV): *m*/*z* (%): 552 (12) $[M]^+$, 224 (16), 223 (31), 106 (13), 105 (100); elemental analysis calcd (%) for $C_{37}H_{28}O_5$: C 80.42, H, 5.11; found: C 80.32, H 5.19.

4,15-Dimethoxy[2.2]paracyclophane (pseudo-*meta*, 18): To a solution of **14** (0.240 g, 1.00 mmol) in DMF (4 mL) NaH (0.088 g, 2.2 mmol, 60% in mineral oil) was added; the resulting brown solution was stirred at room temperature for 2 h and MeI (0.3 mL, 0.710 g, 5 mmol) was added. The reaction mixture was stirred for additional 2 h, diluted with H_2O (30 mL), extracted with Et_2O (5×30 mL), dried with Na_2SO_4. After evaporation of the solvent, the solid residue was purified by preparative chromatography on silica gel (CH_2Cl_2) to furnish **18** (0.215 g, 80%). M.p. 175°C (lit.[23] m.p. 175–177°C).

***para*-Regioselective diacylation of 4,16-dimethoxy[2.2]paracyclophane (18) with acetyl chloride**: To a solution of **18** (0.11 g, 0.41 mmol) in CH_2Cl_2 (10 mL) $TiCl_4$ (0.27 mL, 2.46 mmol) and acetyl chloride (0.18 mL, 2.6 mmol) were added successively at 0°C, and the resulting solution was stirred at room temperature for 10 h. Then $TiCl_4$ (0.27 mL, 2.46 mmol) and acetyl chloride (0.18 mL, 2.6 mmol) were added and the reaction mixture was stirred for further 10 h. The mixture was diluted with water (20 mL) and vigorously stirred for 45 min. The organic layer was washed with H_2O (2×10 mL) and dried with Na_2SO_4. The removal of the solvent in vacuo followed by purification of the crude product by preparative chromatography on silica gel (C_6H_6) yielded **32** (0.10 g, 71%); analytically pure **32** was obtained by recrystallization from toluene.

1,1′-[7,12-Dimethoxy[2.2]paracyclophane-4,15-diyl]diethanone (bis-(*para*)-pseudo-*meta*, 32): M.p. 139–141°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.45 (s, 6H, 2CH_3), 2.66–2.78 (m, 2H, bridge-CH_2), 2.94–3.05 (m, 2H, bridge-CH_2-), 3.17–3.29 (m, 2H, bridge-CH_2-), 3.66 (s, 6H, 2 OCH_3), 3.76–3.88 (m, 2H, bridge-CH_2-), 5.77 (s, 2H, 5-, 16-H or 8-, 13-H), 7.11 ppm (s, 2H, 8-, 13-H or 5-, 16-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 24.86, 25.23, 31.27, 50.72, 112.40, 123.07, 127.19, 127.58, 141.12, 156.56, 195.80 ppm; MS (70 eV): *m*/*z* (%): 353 (56) $[M]^+$, 352 (81) $[M]^+$, 351 (31), 337 (15), 334 (15), 191 (13), 189 (20), 178 (31), 177 (77), 176 (95), 175 (100), 174 (16), 169 (10), 165 (11), 163 (13), 162 (11), 161 (52), 148 (30), 147 (86),

146 (70), 145 (35), 135 (10), 133 (25), 132 (15), 131 (55), 128 (10), 119 (28), 118 (26), 117 (46), 116 (12), 115 (32), 105 (37), 104 (22), 103 (50); elemental analysis calcd (%) for $C_{22}H_{24}O_4$: C 74.98, H 6.86; found: C 74.99, H 6.97.

[2.2]Paracyclophane-4,15-dicarboxylic acid (pseudo-*meta*, 19): To a solution of **9** (5.00 g, 13.66 mmol) in Et_2O (250 mL), *n*BuLi (10 mL, 3.27 N solution in hexane, 32.76 mmol) was added at 20 °C. After stirring the reaction mixture for 3 h a considerable excess of solid CO_2 was added, the resulting mixture was allowed to warm up to room temperature and diluted with H_2O (150 mL). The aqueous phase was separated, the organic phase was washed with H_2O (100 mL), aq. NaOH (3 g in 100 mL of H_2O), H_2O (100 mL) and acidified with 2 N HCl up to pH 1. The precipitate was filtered off, dissolved in 1 N aq. NaOH, the solution was filtered and acidified with 2 N HCl. The precipitate formed was filtered off, thoroughly washed with H_2O (1 L) and dried in vacuo to afford diacid **19** (3.00 g, 74 %). M.p. 283 °C (lit.[41] m.p. 283–283.5 °C).

Dimethyl[2.2]paracyclophane-4,15-dicarboxylate (pseudo-*meta*, 20): To a suspension of **19** (1.00 g, 3.38 mmol) in $CHCl_3$ (30 mL), SO_2Cl_2 (1 mL, 13.5 mmol) was added and the mixture was refluxed for 0.5 h; then DMF (three drops) was added and the mixture was refluxed for additional 1.5 h. The cooled mixture was concentrated, diluted with $CHCl_3$ (10 mL), and MeOH (10 mL) was added. The reaction mixture was stirred under reflux for 1.5 h. After removal of the solvent in vacuo, the residue was purified by preparative chromatography (silica gel, CH_2Cl_2) to yield **20** (0.85 g, 78 %). M.p. 115.5 °C (lit.[10a] m.p. 115 °C).

pseudo-*gem*-Regioselective monoformylation of dimethyl [2.2]paracyclophane-4,15-dicarboxylate (pseudo-*meta*, 20): To a solution of **20** (0.090 g, 0.28 mmol) in CH_2Cl_2 (3 mL), $TiCl_4$ (0.12 mL, 1.11 mmol) and CH_3OCHCl_2 (0.06 mL, 0.67 mmol) were added successively at 0 °C. The resulting solution was stirred at room temperature for 13 d with the alkylating reagent and $TiCl_4$ being added three more times. The reaction mixture was diluted with CH_2Cl_2 (5 mL), cooled to 0 °C, and H_2O (5 mL) and 2 N HCl (5 mL) were successively added. The organic layer was washed with H_2O (2×10 mL), $NaHCO_3$ solution, and dried with Na_2SO_4. After removal of the solvent in vacuo the mixture was separated by preparative chromatography on silica gel (CH_2Cl_2/MeOH 30:1) to yield **35** (0.048 g, 49 %) and recovered **20** (0.036 g, 40 %). An analytically pure sample of **35** was obtained by recrystallization from hexane.

Dimethyl 8-formyl[2.2]paracyclophane-4,15-dicarboxylate (35): M.p. 116.5–117 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.98–3.27 (m, 6H, bridge-CH_2-), 3.82 (s, 3H, -CH_3), 3.96 (s, 3H, -CH_3), 4.01–4.16 (m, 2H, bridge-CH_2-), 6.67 (d, ^3J = 7.8 Hz, 1H, 15-H), 6.71 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1H, 16-H), 7.11, 7.29, 7.31 ppm (3d, ^4J = 1.8 Hz, 3H, 5-, 7-, 12-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 24.88, 30.16, 30.46, 31.49, 47.97, 48.27, 126.75, 129.35, 130.32, 130.79, 131.54, 131.63, 134.51, 135.83, 135.89, 135.92, 138.30, 142.85, 162.60, 162.83, 185.12 ppm; MS (70 eV): *m*/*z* (%): 353 (21) $[M]^+$, 352 (68) $[M]^+$, 205 (12), 203 (13), 202 (23), 201 (11), 191(24), 190 (87), 177 (11), 176 (14), 175 (11), 165 (11), 164 (11), 163 (52), 162 (100), 161 (14), 159 (15), 148 (19), 147 (95), 146 (11), 145 (15), 132 (44), 131 (87), 130 (24), 129 (16), 119 (71), 118 (18), 117 (10), 115(23), 104 (77), 103 (75), 102 (43); elemental analysis calcd (%) for $C_{21}H_{20}O_5$: C 71.58, H 5.72; found: C 71.73, H 5.85.

pseudo-*gem*-Regioselective monobromination of dimethyl [2.2]paracyclophane-4,15-dicarboxylate (pseudo-*meta*, 20): The reaction was carried out in a light-protected reaction vessel. A solution of Br_2 (0.05 mL, 0.9 mmol) in CCl_4 (2 mL) was prepared, and 0.3 mL of this solution was stirred with suspended iron powder (0.03 g, 0.54 mmol) in CH_2Cl_2 (5 mL) for 1 h. Then **20** (0.12 g, 0.37 mmol) in CH_2Cl_2 (15 mL) was added in one portion and the remaining Br_2/CH_2Cl_2 solution was added dropwise. The resulting mixture was stirred at room temperature for 3 d. The reaction mixture was washed with H_2O, aq. Na_2CO_3 and dried with Na_2SO_4. The solvent was removed in vacuo and the solid residue was purified by preparative chromatography on silica gel (CH_2Cl_2) to yield **36** (0.12 g, 80 %).

Dimethyl 8-bromo[2.2]paracyclophane-4,15-dicarboxylate (36): M.p. 149.5–151 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.96–3.34 (m, 5H, bridge-CH_2-), 3.64–3.77 (m, 1H, bridge-CH_2-), 3.87–3.94 (m, 1H, bridge-CH_2-), 3.96 (s, 3H, CH_3), 3.99 (s, 3H, CH_3), 4.33–4.45 (m, 1H, bridge-CH_2-), 6.67 (d, ^3J = 7.8 Hz, 1H, 15-H), 6.74 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1H, 16-H), 6.87 (d, ^4J = 1.8 Hz, 1H, 7-H), 7.20 (d, ^4J = 1.8 Hz, 1H, 12-H), 7.45 ppm (d, ^3J = 1.8 Hz, 1H, 5-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 29.66, 30.05, 30.61, 30.72, 47.65, 48.28, 124.52, 125.15, 129.25, 129.91, 130.51, 130.76, 131.84, 135.06, 135.55, 136.70, 137.60, 139.16, 162.73, 163.07 ppm; HRMS: calcd for $C_{20}H_{19}O_4Br$: *m*/*z*: 402.0467 $[M]^+$; found: 402.0452.

pseudo-*gem*-Regioselective dibromination of dimethyl [2.2]paracyclophane-4,15-dicarboxylate (pseudo-*meta*, 20): The reaction was carried out as described above for the monobromination of **20**. After 3 d an excess of Br_2 (0.15 mL, 2.7 mmol) was added and the reaction mixture was stirred at room temperature for further 10 d. The reaction mixture was washed with H_2O, aq. Na_2CO_3 and dried with Na_2SO_4. The solvent was removed in vacuo and the solid residue was purified by preparative chromatography on silica gel with CH_2Cl_2 to produce **37** (0.17 g, 93 %). An analytically pure sample of **37** was obtained by recrystallization from hexane.

An improved synthesis of 37: A solution of Br_2 (0.56 mL, 1.1 mmol) in CCl_4 (1 mL) was stirred with suspended iron powder (0.030 g, 0.54 mmol) in a light-protected reaction vessel for 1 h. Then **20** (0.035 g, 0.11 mmol) in CH_2Cl_2 (4 mL) and a solution of Br_2 (0.56 mL, 1.1 mmol) in CCl_4 (1 mL) were added in one portion. The resulting mixture was refluxed for 10 h, washed with H_2O, aq. Na_2CO_3 and dried with Na_2SO_4. The solvent was removed in vacuo and the solid residue was purified by preparative chromatography on silica gel (CH_2Cl_2) to yield **37** (0.046 g, 88 %).

Dimethyl 8,13-dibromo[2.2]paracyclophane-4,15-dicarboxylate (bis-(pseudo-*gem*)-pseudo-*meta*-, 37): M.p. 170.5–171 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.94–3.14 (m, 4H, bridge-CH_2-), 3.40–3.52 (m, 2H, bridge-CH_2-), 3.91 (s, 6H, 2-CH_3), 4.27–4.39 (m, 2H, bridge-CH_2-), 6.78 (d, ^4J = 1.8 Hz, 2H, 5- and 16-H), 7.41 ppm (d, ^4J = 1.8 Hz, 2H, 7- and 12-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 27.70, 28.81, 48.07, 125.82, 127.30, 128.63, 135.16, 135.82, 137.95, 162.46 ppm; MS (70 eV): *m*/*z* (%): 483 (32) $[M]^+$, 482 (15) $[M]^+$, 481 (59) $[M]^+$, 479 (31), 466 (13), 243 (29), 242 (100), 240 (100), 239 (11), 227 (36), 226 (12), 225 (50), 223 (15), 211 (45), 210 (14), 209 (27), 203 (10), 202 (22), 201 (13), 200 (18), 199 (43), 198 (12), 197 (46), 189 (16), 184 (32), 183 (13), 182 (33), 162 (12), 129 (14), 115 (12), 104 (10), 103 (38), 102 (87); elemental analysis calcd (%) for $C_{20}H_{18}Br_2O_4$: C 49.82, H 3.76, Br 33.14; found: C 49.64, H 3.64, Br 33.28.

Dimethyl 7,13-dibromo[2.2]paracyclophane-4,16-dicarboxylate (bis-(pseudo-*gem*)-pseudo-*para*-, 41): Compound **41** was obtained by the same method as that described above from dimethyl[2.2]paracyclophane-4,16-dicarboxylate **40** (0.200 g, 0.617 mmol) in 97 % chemical yield (0.288 g). An analytically pure sample was obtained by recrystallization from heptane/toluene (0.214 g, 72 %). M.p. 235–236 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.86–3.07 (m, 4H, bridge-CH_2), 3.48–3.67 (m, 2H, bridge-CH_2), 3.90 (s, 6H, 2 CH_3), 4.29–4.43 (m, 2H, bridge-CH_2), 6.72 (s, 2H, 5-, 15-H or 8-, 12-H), 7.37 ppm (s, 2H, 8-, 12-H or 5-, 15-H); NMR ^{13}C (151 MHz, $CDCl_3$): δ = 32.53(2C, bridge), 34.71 (2C, 2 CH_3, 2 C-bridge), 128.32, 130.99, 153.71, 138.87 (4C), 143.89, 166.55 ppm (2COO); MS (70 eV): *m*/*z* (%): 484 (40) $[M]^+$, 483 (19) $[M]^+$, 482 (75) $[M]^+$, 481 (10) $[M]^+$, 480 (37) $[M]^+$, 469 (11), 467 (16), 371 (37) $[M-CH_3]^+$, 370 (10) $[M-CH_3]^+$, 369 (36) $[M-CH_3]^+$, 243 (11) $[M/2]^+$, 242 (97), 241 (37), 240 (100), 239 (26), 227 (21), 225 (28), 212 (24), 211 (12), 210 (31), 202 (11), 199 (15), 197 (19), 184 (19), 182 (17),103 (10), 102 (20), 101 (10); elemental analysis calcd (%) for $C_{20}H_{18}Br_2O_4$: C 49.82, H 3.76, Br 33.14; found: C 50.26, H 3.92, Br 33.35.

***ortho*-Regioselective diacylation of [2.2]paracyclophane-4,16-diol (pseudo-*para*-, 12) with acetyl chloride**: Compound **38** was obtained from 0.20 g (0.83 mmol) of **12** in an isolated yield of 0.24 g (89 %) using the method as described for the acylation of **14**.

1,1′-[5,15-Dihydroxy[2.2]paracyclophane-4,16-diyl]diethanone (bis-(*ortho*)-pseudo-*para*, 38): Decomp. temp. 210–212 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.32–2.45 (m, 2H, bridge-CH_2-), 2.60 (s, 6H, 2 -CH_3), 3.17–3.31 (m, 2H, bridge-CH_2-), 3.39–3.49 (m, 2H, bridge-CH_2-), 3.50–3.61 (m, 2H, bridge-CH_2-), 6.39 (d, ^3J = 7.8 Hz, 2H, 7-, 13-H or 8-, 12-H), 6.62 (d, ^3J = 7.8 Hz, 2H, 8-, 12-H or 7-, 13-H), 12.80 ppm (s, 2H, 2OH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 26.97, 27.38, 30.90, 118.47, 120.44, 123.27, 133.69, 139.14, 158.52, 200.66 ppm; MS (70 eV): *m*/*z* (%): 324 (64) $[M]^+$, 306 (37), 291 (14), 281 (12), 189 (12), 161 (100), 153 (12),

147 (61), 133 (66), 119 (65), 115 (51), 105 (36); elemental analysis calcd (%) for $C_{20}H_{20}O_4$: C 74.06, H 6.21; found: C 74.13, H 6.33.

General procedure for the synthesis of the Schiff bases of bis-acetylhydroxy[2.2]paracyclophanes (21 or 38): To a solution of bis-acetylhydroxy[2.2]paracyclophane (**21** or **38**, 0.72 mmol) in toluene (30 mL) enantiomerically pure α-PEAM (0.22 mL, 1.8 mmol) and a catalytic amount of Et_2SnCl_2 were added. The reaction mixture was refluxed for 40 h in a flask equipped with a Dean-Stark trap filled with $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was subjected to preparative chromatography on silica gel.

Separation of the diastereomeric Schiff bases of 21 with (*R*)-α-PEAM: The equimolar mixture of diastereomeric (R,R_p,R)- and (R,S_p,R)-**25** was separated by preparative chromatography on silica gel (toluene/EtOH 20:1) to produce 0.18 g (92%) of diastereomerically pure (R,S_p,R)-**25** (R_f = 0.60) and 0.16 g (84%) of diastereomerically pure (R,R_p,R)-**25** (R_f = 0.45).

(R,S_p,R)-4,15-Dihydroxy-5,16-[di-1-(1-phenylethylimino)ethyl][2.2]paracyclophane (bis-(*ortho*)-pseudo-*meta*, (R,S_p,R)-25): Decomp. temp. 230–235 °C; $[\alpha]_D^{25}$ = +914.7° (c = 0.23 in toluene); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.75 (d, 6H, 2 CH_3, ^3J = 6.5 Hz), 2.29 (2s, 6H, 2 CH_3), 2.38–2.51 (m, 2H, bridge-CH_2-), 2.71–2.84 (m, 2H, bridge-CH_2-), 3.22–3.34 (m, 2H, bridge-CH_2-), 3.38–3.51 (m, 2H, bridge-CH_2-), 4.89 (q, 2H, 2 CH, ^3J = 6.5 Hz), 6.06 (d, ^3J = 7.8 Hz, 2H, 7-, 12-H or 8-, 13-H), 6.95 (d, ^3J = 7.8 Hz, 2H, 8-, 13-H or 7-, 12-H), 7.21–7.29 (m, 2H, Ph), 7.31–7.40 (m, 8H, Ph), 15.89 ppm (s, 2H, 2 OH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 15.92, 21.36, 24.97, 33.89, 54.28, 116.97, 120.05, 122.25, 123.13, 124.82, 125.58, 126.87, 134.30, 139.80, 158.96, 166.37 ppm; MS (70 eV): m/z (%): 530 (2) $[M]^+$, 409 (17), 304 (8), 265 (16), 161 (41), 160 (56), 132 (11), 105 (100), 104 (20); elemental analysis calcd (%) for $C_{36}H_{38}N_2O_2$: C 81.48, H 7.22, N 5.28; found: C 81.63, H 7.35, N 5.22.

(R,R_p,R)-4,15-Dihydroxy-5,16-[di-1-(1-phenylethylimino)ethyl][2.2]paracyclophane (bis-(*ortho*)-pseudo-*meta*, (R,R_p,R)-25): M.p. 74–75 °C; $[\alpha]_D^{25}$ = +238.8° (c = 0.17 in toluene); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.67 (d, 6H, 2CH_3, ^3J = 6.5 Hz), 1.98–2.11 (m, 2H, bridge-CH_2-), 2.22 (s, 6H, 2CH_3), 2.69–2.87 (m, 2H, bridge-CH_2-), 3.06–3.20 (m, 2H, bridge-CH_2-), 3.22–3.36 (m, 2H, bridge-CH_2-), 4.85 (q, ^3J = 6.5 Hz, 2H, 2 CH), 5.65 (d, ^3J = 7.8 Hz, 2H, 7-, 12-H or 8-, 13-H), 6.88 (d, ^3J = 7.8 Hz, 2H, 8-, 12-H or 7-, 13-H), 7.27–7.36 (m, 2H, Ph), 7.40–7.48 (m, 4H, Ph), 7.55 (d, ^3J = 7.5 Hz, 4H, 4 *ortho*-Ph), 15.91 ppm (s, 2H, 2 OH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.72, 24.82, 28.93, 37.70, 58.22, 120.90, 124.28, 126.57, 127.31, 128.81, 129.34, 130.66, 138.41, 144.49, 162.97, 169.97 ppm; MS (70 eV): m/z (%): 530 (24) $[M]^+$, 425 (17), 409 (48), 304 (46), 288 (36), 265 (65), 160 (82), 146 (20), 132 (24), 105 (100); elemental analysis calcd (%) for $C_{36}H_{38}N_2O_2$: C 81.48, H 7.22, N 5.28; found: C 81.43, H 7.20, N 5.20.

((S,{R_p,S_p},S)-5,15-[Bis-*N*-(1-phenylethyl)ethanimidoyl][2.2]paracyclophane-4,16-diol (internal diastereomer, (S,{R_p,S_p},S)-**39**) was obtained by purification of the reaction mixture on silica gel (CH_2Cl_2/Et_2O 10:1) with a chemical yield of 0.33 g (86%); m.p. 79–80 °C; $[\alpha]_D^{25}$ = −130.7° (c = 0.28 in toluene); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.74 (d, ^3J = 6.5 Hz, 3H, CH_3), 1.79 (d, ^3J = 6.5 Hz, 3H, CH_3), 1.97–2.13 (m, 1H, bridge-CH_2-), 2.26–2.48 (m, 1H, bridge-CH_2-), 2.39 (s, 6H, 2 -CH_3), 3.08–3.57 (m, 6H, bridge-CH_2-), 4.87–5.04 (m, 2H, 2 -CH-), 6.08 (d, ^3J = 7.8 Hz, 1H, 7- or 13- or 8- or 12-H,), 6.45 (d, ^3J = 7.8 Hz, 1H, 7- or 13- or 8- or 12-H), 6.56 (d, ^3J = 7.8 Hz, 7- or 13- or 8- or 12-H), 6.60 (d, ^3J = 7.8 Hz, 1H, 7- or 13- or 8- or 12-H), 7.25–7.63 (m, 10H, 2 Ph), 15.82 (brs, 1H, OH), 16.02 ppm (brs, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.32, 16.47, 20.93, 21.43, 27.44, 27.64, 30.94, 30.98, 54.14, 54.26, 117.95, 118.05, 119.05, 119.12, 122.28, 122.46, 123.14, 123.32, 124.84 (2C), 129.09, 129.54, 137.24, 137.50, 139.85, 140.56, 158.74, 159.03, 166.60, 166.81 ppm; MS (70 eV): m/z (%): 530 (17) $[M]^+$, 425 (37), 409 (31), 304 (12), 265 (45), 160 (82), 146 (21), 132 (33), 105 (100); HRMS: calcd for $C_{36}H_{38}O_2N_2$: m/z: 530.2933 $[M]^+$; found: 530.2687.

Synthesis and separation of the diastereomeric Schiff bases of 22: To a solution of **22** (0.09 g, 0.32 mmol) in toluene (6 mL) enantiomerically pure (*R*)-α-PEAM (0.05 mL, 0.38 mmol) and a catalytic amount of Et_2SnCl_2 were added. The reaction mixture was refluxed for 3 h in a flask equipped with a Dean-Stark trap filled with $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was subjected to preparative chromatography on silica gel. MS (70 eV): m/z (%): 386 (46) $[M]^+$, 385 (71) $[M]^+$, 280 (19), 266 (45), 265 (79), 264 (61), 263 (17), 250 (22), 249 (12), 174 (12), 162 (50), 161 (91), 160 (96), 159 (17), 133 (23), 132 (44), 131 (13), 130 (14), 122 (45), 121 (10), 120 (42), 118 (20), 117 (21), 116 (11), 115 (28), 107 (11), 106 (49), 105 (100), 104 (41), 103 (50). The equimolar mixture of diastereomeric (R_p,R)- and (S_p,R_c)-**26** was separated by preparative chromatography on silica gel (CH_2Cl_2/Et_2O 10:1) to produce 0.052 g (85%) of diastereomerically pure (S_p,R)-**26** (R_f = 0.32, CH_2Cl_2/Et_2O/Et_3N 10:1:0.1) and 0.056 g (91%) of diastereo-merically pure (R_p,R)-**26** (R_f = 0.23, CH_2Cl_2/Et_2O/Et_3N 10:1:0.1).

(S_p,R)-4,15-Dihydroxy-5[1-(1-phenylethylimino)-ethyl][2.2]paracyclophane 26 ((S_p,R)-26): An analytically pure sample was obtained by recrystallization from a toluene/hexane mixture. M.p. 154.0–154.5 °C; $[\alpha]_D^{25}$ = −453.4° (c = 0.31 in toluene); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.75 (d, ^3J = 6.5 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.46–2.58 (m, 1H, bridge-CH_2-), 2.61–2.72 (m, 1H, bridge-CH_2-), 2.75–2.86 (m, 1H, bridge-CH_2-), 2.87–3.07 (m, 2H, bridge-CH_2-), 3.11–3.21 (m, 1H, bridge-CH_2-), 3.24–3.36 (m, 1H, bridge-CH_2-), 3.38–3.49 (m, 1H, bridge-CH_2-), 4.43 (brs, 1H, C-15(OH)), 4.89 (q, ^3J = 6.5 Hz, H, = N-CH), 5.70 (d, ^4J = 1.8 Hz, 1H, 16-H), 6.11 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1H, 12-H), 6.17, 6.89, 6.95 (3d, ^4J = 7.8 Hz, 3H, 13-, -7, 8-H), 7.13–7.40 (m, 5H, Ph), 15.91 ppm (s, 1H, C(4)-OH); elemental analysis calcd (%) for $C_{26}H_{27}NO_2$: C 81.01, H 7.06, N 3.63; found: C 81.10, H 7.23, N 3.37.

(R_p,R)-4,15-Dihydroxy-5[1-(1-phenylethylimino)ethyl][2.2]paracyclophane 26 ((R_p,R)-26): An analytically pure sample was obtained by recrystallization from heptane; m.p. 178 °C; $[\alpha]_D^{25}$ = +103.7° (c = 0.19 in toluene); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.75 (d, ^3J = 6.5 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.46–2.58 (m, 1H, bridge-CH_2-), 2.61–2.72 (m, 1H, bridge-CH_2-), 2.75–2.86 (m, 1H, bridge-CH_2-), 2.87–3.07 (m, 2H, bridge-CH_2-), 3.11–3.21 (m, 1H, bridge-CH_2-), 3.24–3.36 (m, 1H, bridge-CH_2-), 3.38–3.49 (m, 1H, bridge-CH_2-), 4.43 (brs, 1H, C-15(OH)), 4.89 (q, ^3J = 6.5 Hz, H, = N-CH), 5.70 (d, ^4J = 1.8 Hz, 1H, 16-H), 6.11 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1H, 12-H), 6.17, 6.89, 6.95 (3d, ^3J = 7.8 Hz, 3H, 13-, 7-, 8-H), 7.13–7.40 (m, 5H, Ph), 15.91 ppm (s, 1H, C-4(OH)); elemental analysis calcd (%) for $C_{26}H_{27}NO_2$: C 81.01, H 7.06, N 3.63; found: C 81.10, H 7.23, N 3.37.

Enantioselective diethylzinc addition to benzaldehyde catalyzed by (R,R_p,R)-25, (R,S_p,R)-25, (S_p,R)-26, (S,{R_p,S_p},S)-39; typical procedure: To a solution of a Schiff base (0.01 mmol) in toluene (0.28 mL), Et_2Zn (0.2 mL of 1.1 M solution in toluene, 0.22 mmol) was added in one portion at 0 °C. Subsequently benzaldehyde (0.1 mmol) was added dropwise and the reaction mixture was stirred for 15 h at room temperature. The mixture was quenched with 1 N HCl (0.45 mL), diluted with Et_2O (2 mL) and H_2O (1 mL). The organic layer was separated, the aqueous layer was extracted with Et_2O (3 × 2 mL) or CH_2Cl_2 (3 × 2 mL) and the combined organic fractions were washed with aq. $NaHCO_3$ (3 mL) and dried over Na_2SO_4. The oily residue obtained after solvent removal was subjected without further purification to chiral HPLC. Enantiomeric analysis of 1-phenylpropanol was performed by HPLC (Varian 5000 LC) on Chiralcel OD (250 mm × 4.6 mm) with hexane/isopropanol 100:4, flow rate 1 mL min^{-1}, temperature 20 °C, detector UV 254 nm: the retention times were 9.4 (*S*) and 11.1 min (*R*), respectively.

X-ray crystallographic study of 21, (R,S_p,R)-25 and (S_p,R)-26: The structures were solved by direct methods and refined by the full-matrix least-squares against F^2 in anisotropic (for non-hydrogen atoms) and isotropic (for H atoms) approximation. All hydrogen atoms (with the exception of the H atoms of OH-and N-H groups) were placed in geometrically calculated positions and included in the final refinement using the riding model with the U_{iso}(H) parameters equal to 1.2U_{eq}(C_i) or 1.5U_{eq}(C_{ii}), where

U(C_i) and U(C_{ii}) are, respectively, the equivalent thermal parameters of the sp^2 and sp^3 carbon atoms to which the respective H atoms are bonded. The H atoms of OH and NH- groups were located from the difference Fourier synthesis and included in the final refinement using the riding model with the U_{iso}(H) parameters equal to 1.2U_{eq}(O_i), where U(O_{ii}) are the equivalent thermal parameters of the oxygen atoms to which respective H atoms are bonded. The analysis of the Fourier electron density synthesis has revealed that toluene solvate molecules are dis-

Table 3. Crystal data and structure refinement parameters for **21**, (R,S_p,R)-**25** and (S_p,R)-**26**.

	21	(R,S_p,R)-**25**	(S_p,R)-**26**
empirical formula	$C_{20}H_{20}O_4$	$C_{36}H_{38}N_2O_2$	$C_{26}H_{27}NO_2$
formula weight	324.36	530.68	431.55
T [K]	120	163	100
crystal system	monoclinic	orthorhombic	tetragonal
size [mm]	$0.6\times0.4\times0.2$	$0.5\times0.4\times0.3$	$0.4\times0.03\times0.03$
space group	$P2_1/n$	$P2_12_12_1$	$P4_3$
$Z(Z')$	4(1)	4(1)	4(1)
a [Å]	7.706(1)	7.841(2)	16.641(2)
b [Å]	14.489(2)	15.280(5)	16.641(2)
c [Å]	14.376(2)	23.705(7)	9.211(2)
α [°]	90.00	90.00	90.00
β [°]	103.573(4)	90.00	90.00
γ [°]	90.00	90.00	90.00
V [Å^3]	1560.2(4)	2840.2(15)	2550.6(7)
ρ_{calcd} [g cm^{-1}]	1.381	1.241	1.124
linear absorption, μ [cm^{-1}]	0.95	0.76	0.7
F(000)	688	1136	924
$2\theta_{max}$ [°]	56	52	52
diffractometer	Smart 1000 CCD	Syntex P21	Smart Apex II CCD
scan type	ω	$\theta/2\theta$	ω
completeness of data set [%]	98.5	98.1	99.4
reflections measured	11687 [R_{int} = 0.0612]	3336 [R_{int} = 0.0104]	19222 [R_{int} = 0.0931]
independent reflections	3686	3298	2787
observed reflections [$I > 2\sigma(I)$]	1843	2835	1874
parameters	217	361	297
$R1$	0.0667	0.0548	0.0621
$wR2$	0.1321	0.1328	0.1708
GOF	1.039	0.981	1.083
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [e Å^{-3}]	0.371/−0.379	0.386/−0.327	0.416/−0.237

ordered by two positions. The disordered toluene molecules were refined as rigid groups in isotropic approximation. Crystal data and structure refinement parameters for **21**, (R,S_p,R)-**25** and (S_p,R)-**26** are given in Table 3. All calculations were performed using the SHELXTL software [G. M. Sheldrick, SHELXTL-97, Version 5.10, Bruker AXS Inc., Madison, WI-53719, USA].

CCDC 614214 (**21**), 614215 [(R_c,S_p,R_c)-**25**] and 626319 [(S_p,R)-**26**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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