Resolution and Novel Reactions of 4-Hydroxy[2.2]paracyclophane

Valeria Rozenberg,*[a] Tat'yana Danilova,[a] Elena Sergeeva,[a] Evgenii Vorontsov,[a] Zoya Starikova,[a] Aleksandr Korlyukov,[a] and Henning Hopf*[b]

Keywords: Chiral resolution / Chirality / Cyclophanes / Oxaloylation / Regioselective *ortho*, *para* substitution / Stereoselective synthesis

The resolution of racemic 4-hydroxy[2.2]paracyclophane (**1**) by fractional crystallization of the diastereomeric esters **3** with (1*S*)-(−)-camphanic acid and the determination of the absolute configurations of (*R*)- and (*S*)-4-hydroxy[2.2]paracyclophanes by X-ray diffraction have been carried out. The Friedel–Crafts oxaloylation of **1** with $AlCl_3$ was found to occur with formation of both *ortho*- and *para*-hydroxy[2.2]paracyclophanylglyoxylic acids, whereas in the presence of $TiCl_4$, quantitative formation of 2,3-dioxo-2,3-dihydrofurano[4,5-*d*][2.2]paracyclophane (**8**) as a product of an unusual cooperative *C*- and *O*-acylation was observed. Replacement of the OH group in the substrate for OCH_3 (compound **18**) changes the regioselectivity of the oxaloylation, which now occurs with formation of a *para*-substituted α-diketone **19**. A novel technique for the synthesis of 4-formyl-5-hydroxy[2.2]paracyclophane (FHPC, **15**) involving stereoselective reduction of **8** followed by oxidative cleavage of the intermediate diol **14** is also presented.

Introduction

The first enantiomerically pure monosubstituted [2.2]paracyclophanes, such as [2.2]paracyclophane-4-carboxylic acid[1] and its derivatives (amide, nitrile, esters), as well as ketones, alcohols, amines, azides, chlorides,[2] and aldehyde,[2,3] were synthesized nearly 30 years ago. During the last few years a number of efficient resolutions and examples of enantioselective syntheses of different chiral mono- and disubstituted [2.2]paracyclophanes have been reported.[4a−4g] The renewal of interest in chiral [2.2]paracyclophanes arises from their application as planar chiral auxiliaries and ligands in stereoselective synthesis.[4a−4c,4e,4f,4i,5a−5l] A number of these compounds are phenols and hence can in principle be obtained in optically pure form by starting from enantiomers of 4-hydroxy[2.2]paracyclophane (**1**). Our recent findings have opened up the possibility of converting enantiomers of **1** into chiral hydroxyaryl ketones by means of *ortho*- or *para*-regioselective Friedel−Crafts acylation or Fries rearrangements.[6] Moreover, enantiomers of **1** could be used as starting materials for the recently synthesized chiral dendrophanes[7] and laterally functionalized [2.2]paracyclophanes.[8]

Two routes to the enantiomers of **1** have previously been described: On the one hand a three-step synthesis of (*R*)-**1** from (*R*)-4-amino[2.2]paracyclophane, which in turn is obtained by resolution of the racemic amine; however, this method is not very efficient because of the quite low overall yield.[9] On the other hand, the lipase-catalyzed enzymatic kinetic resolution of 4-acetoxy[2.2]paracyclophane (**2**), independently proposed by two groups,[10,11] is more effective. Thus, under optimal conditions, the resolution of 0.6 mmol of racemic **2** resulted in optically pure (*S*)-**2** (*ee* > 99%, chem. yield 44%) and (*R*)-**1** (*ee* 90%, chem. yield 51%). Screening of 28 different lipases showed that *Candida rugosa* (formerly *Candida cylindracea*) was the best enzyme for kinetic resolution of **2**.[4g] However, the authors also showed that the lipase employed should be obtained from a specific supplier (Amano), because at least two additional, unwanted lipases were found in *Candida cylindracea* preparations from other commercial providers. Furthermore, the enzymatic resolution required special equipment and skill and so is less than ideal for use by organic chemists on a routine basis.

We therefore decided to develop a new and effective chemical resolution technique for 4-hydroxy[2.2]paracyclophane (**1**) by way of diastereomeric derivatives. The successful result of this approach is presented in this publication. Furthermore, in continuation of our research on regioselective acylation of **1**, we have investigated the oxaloylation of phenol **1** and its methoxy derivative. Finally, we propose a

[a] A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Science,
Vavilova 28, 119991 Moscow, Russia
Fax: (internat) + 7-095/135-5085
E-mail: lera@ineos.ac.ru
[b] Institute of Organic Chemistry, Technical University of Braunschweig,
Hagenring 30, 38106, Germany
Fax: (internat) + 49-531/535-388
E-mail: H.Hopf@tu-bs.de

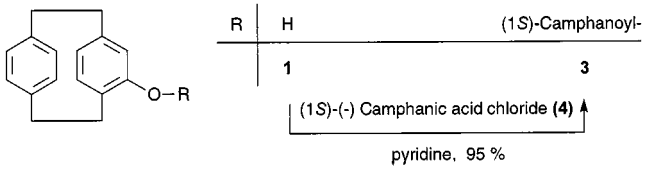
  1434−193X/02/0203−0468 $ 17.50+.50/0 *Eur. J. Org. Chem.* **2002**, 468−477

new simple and effective method for the preparation of 4-formyl-5-hydroxy[2.2]paracyclophane (FHPC).

Results and Discussion

Resolution of 4-Hydroxy[2.2]paracyclophane (1) into Enantiomers

As a new reagent for resolution of **1** into enantiomers, we propose (1*S*)-(−)-camphanic acid, the lactone of 1-hydroxy-2,2,3-trimethylcyclopentane-1,3-dicarboxylic acid, which has also been employed as a resolving reagent for the resolution of other phenols[12] and alcohols.[13] Diastereomeric esters **3** (Scheme 1) were obtained in high chemical yield (95%) by treatment of **1** with commercially available (1*S*)-(−)-camphanoyl chloride (**4**) [it may also be synthesized from (1*S*)-(−)-camphanic acid and thionyl chloride[14]] in pyridine. Initially, the reaction was carried out with 1.8 equiv. (excess) of the acyl chloride according to the reported technique.[12] Later we found that the reaction occurs smoothly over 1 h at room temperature with equimolar amounts of **1** and **4**. According to ^{1}H NMR spectroscopic data, the diastereomeric esters **3** were formed in a 1:1 ratio.



Scheme 1

The separation of the diastereomeric esters **3** was carried out by fractional crystallization. We found that crystallization from ethyl acetate gave 12−14% of (R_p,1*S*)-**3** (*de* > 95% according to ^{1}H NMR analysis) as a first crop and 10−12% of (S_p,1*S*)-**3** (*de* > 91% according to ^{1}H NMR analysis) as a second crop from the same solution. The filtrate was concentrated and the crystallization procedure was repeated twice. The combined fractions enriched in (R_p,1*S*)-**3** or (S_p,1*S*)-**3**, respectively, were separately recrystallized from ethyl acetate to yield (R_p,1*S*)-**3** (19.4%, *de* 97%, $[\alpha]_D^{25}$ = −24.14) and (S_p,1*S*)-**3** (19−19.6%, *de* 97−99%, $[\alpha]_D^{25}$ = +24.78). The diastereomeric purity of (R_p,1*S*)-**3** was improved to 99% by crystallization from the same solvent. Combined filtrates containing the two diastereomers in equal amounts (according to the ^{1}H NMR spectrum) were reused for the resolution. To liberate the pure enantiomers of **1**, (R_p,1*S*)-**3** and (S_p,1*S*)-**3** were reduced with $LiAlH_4$ in THF in a Soxhlet apparatus. Enantiomers (*R*)- and (*S*)-**1** were obtained in 92−94% chemical yields; their enantiomeric purities were determined as > 99% by GC on a chiral column. The absolute configurations of (*R*)- and (*S*)-**1** were determined by X-ray diffraction analysis of the camphanic acid esters **3**; the results are shown in Figure 1.

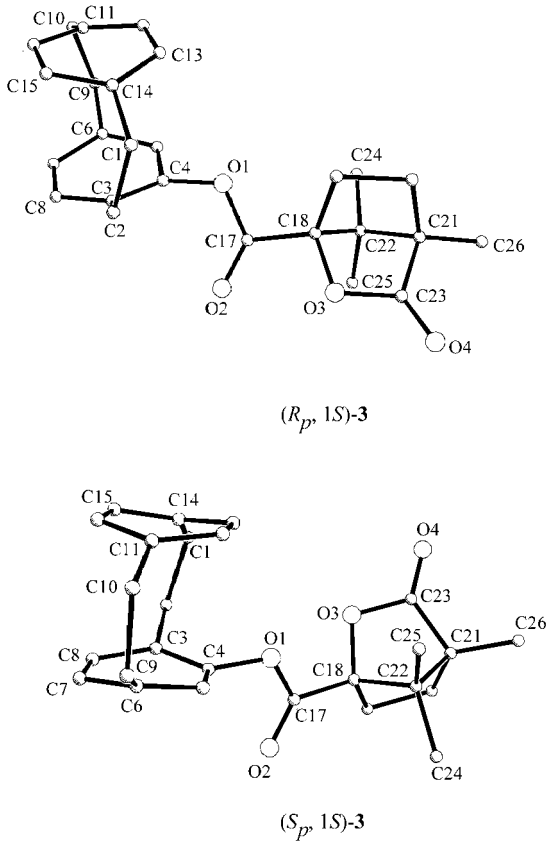


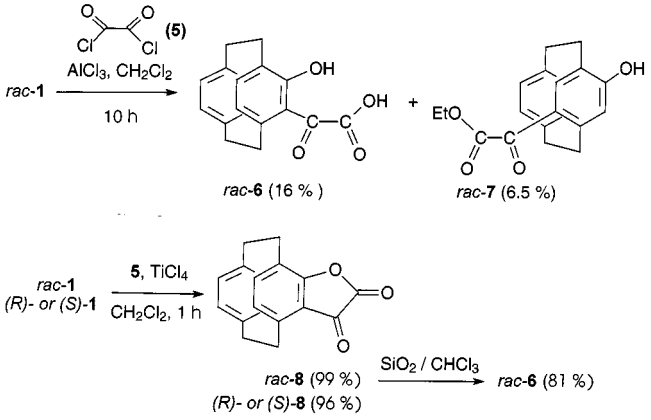
Figure 1. X-ray structures of the diastereomeric esters **3** of 4-hydroxy[2.2]paracyclophane with (1*S*)-(−)-camphanic acid

Regioselective Oxaloylation of 4-Hydroxy[2.2]-paracyclophane (1)

Oxaloylation of classical phenols under common Friedel−Crafts conditions ($AlCl_3$ in CH_2Cl_2) is not regioselective and is usually accompanied by competition between *ortho*-, *para*-acylation, bis(arylation), and decarbonylation side reactions.[15] For example, treatment of phenol with oxalyl chloride in the presence of $AlCl_3$ produces 2-hydroxyphenylglyoxylic acid (20%) together with 2,2′- and 2,4′-dihydroxybenzil (13 and 7%, respectively), and a considerable quantity of unidentified products.[16] To achieve *ortho*-regioselective synthesis of the target 2-hydroxyphenylglyoxylic acids, an approach involving oxaloylation of different bromomagnesium phenolates has been proposed.[16] It was also shown that the oxaloylation occurs *ortho*-regioselectively in the presence of sterically hindered *meta* substituents in the phenol.[17]

We started our study on the regioselectivity of the direct oxaloylation of **1** by applying standard conditions ($AlCl_3$, CH_2Cl_2; Scheme 2). The reaction was not complete even after 2 d at room temperature. Preparative chromatography of the reaction mixture allowed the recovery of the starting material (47%) and provided two new compounds, which were identified by ^{1}H NMR and mass spectrometry as (4-hydroxy[2.2]paracyclophan-5-yl)glyoxylic acid (**6**) (16%) and ethyl (4-hydroxy[2.2]paracyclophan-7-yl)glyoxylate (**7**)

(6.5%). The formation of **7** can be explained by the reaction of the corresponding intermediate acyl chloride with traces of EtOH present in the diethyl ether used for workup of the reaction mixture. In support of this assumption, (methyl [2.2]paracyclophan-4-yl)glyoxylate was formed when the oxaloylation of the parent [2.2]paracyclophane ($AlCl_3$, CH_2Cl_2, −10 °C) was followed by treatment with methanol.[18]

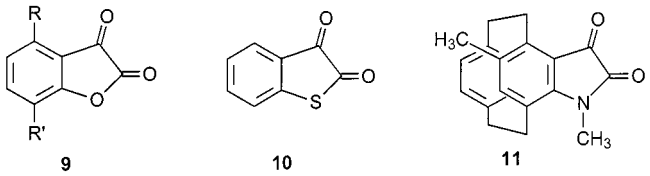


Scheme 2

When the oxaloylation of **1** was carried out under conditions that had been found to be optimal for its *ortho*-regioselective acylation with acyl chlorides ($TiCl_4$, CH_2Cl_2, room temperature),[6] the reaction was complete within 1 h (Scheme 2). The sole product formed in this reaction, in quantitative yield, was purified by crystallization from heptane and identified by spectroscopic and analytical data and X-ray structural analysis as 2,3-dioxo-2,3-dihydrofurano[4,5-*d*][2.2]paracyclophane (**8**). The cyclic ester **8** is very stable towards the action of aqueous or/and alcoholic acid and base solutions. However, **8** is unstable on silica gel, suffering ring-opening to give the corresponding (*ortho*-hydroxy[2.2]paracyclophanyl)glyoxylic acid **6** (81%).

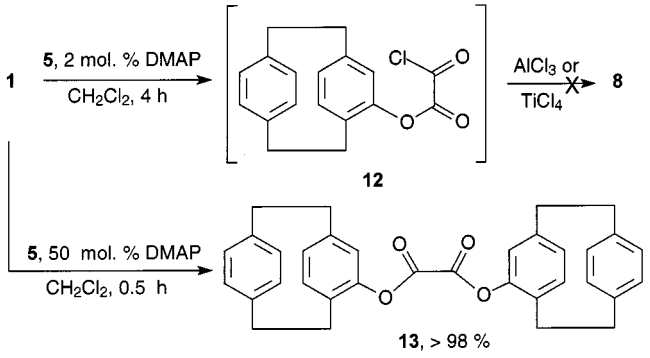
To the best of our knowledge, there are no previous examples of formation of cyclic compounds such as **8** by direct Friedel−Crafts oxaloylation of phenols. When we carried out the oxaloylation of thymol (2-isopropyl-5-methylphenol) under the same conditions, a complex mixture of at least six different compounds was formed, from which (2-hydroxy-3-isopropyl-6-methylphenyl)oxoacetic acid (16%) together with bis(4-hydroxy-5-isopropyl-2-methylphenyl) diketone (3%) were isolated in quantities large enough for analysis.

For the synthesis of 4,7-disubstituted 2,3-dihydrobenzofuran-2,3-diones **9** (Scheme 3) from sterically hindered 2,5-disubstituted phenols, a two-step procedure involving initial *O*-acylation with excess oxalyl chloride in the presence of a catalytic amount of DMAP followed by $AlCl_3$-promoted Friedel−Crafts ring-closure has been suggested.[19] Application of this procedure to thiophenol produced the corresponding 2,3-dihydrobenzothiophene-2,3-dione (**10**).[20] One example of *N*-oxaloylation of racemic *para*-substituted 4-(methylamino)[2.2]paracyclophane with further formation of 2,3-dihydro-2,3-dioxopyrrolo[4,5-*d*][2.2]paracyclophane **[11]** by use of $AlCl_3$ has also been described.[21]



Scheme 3

Our previous attempts to synthesize **8** from 4-hydroxy-[2.2]paracyclophane (**1**) by the approach described above met with failure; on treatment of **1** with **5** in the presence of catalytic amounts of DMAP (2 mol %) the starting material was consumed with probable formation of the intermediate product **12**. However, on subjection to $AlCl_3$ or $TiCl_4$, neither the desired cyclic product **8** nor any other identifiable compounds were formed. All attempts to isolate, purify, and identify an intermediate **12** failed, although similar derivatives of normal aromatic phenols are quite stable and could be isolated by distillation under reduced pressure without decomposition.[19a] On increasing the DMAP concentration to 50 mol %, we observed the formation of the dimeric *O*-oxaloylated product **13** (Scheme 4) in quantitative yield even with a twofold excess of oxalyl chloride.



Scheme 4

Bis([2.2]paracyclophan-4-yl) oxalate (**13**) was isolated in high chemical yield and characterized by the usual analytical data (see Exp. Sect.). With two chiral [2.2]paracyclophane moieties, compound **13** should in principle be obtained as a mixture of two diastereomers (*chiral* and *meso*). Only one set of signals was observed in the ^1H NMR spectrum of the reaction mixture, though. In the ^{13}C NMR spectrum, however, two sets of signals of equal integral intensity were detected at δ = 32.32 and 32.35 for C-2 and at δ = 156.17 and 156.25 for C-17=O, proving the formation of an equimolar mixture of the diastereomeric compounds **13**.

X-ray Diffraction Study of Racemic 2,3-Dihydro-2,3-dioxofurano[4,5-*d*][2.2]paracyclophane (8)

The X-ray diffraction study was carried out with single crystals of racemic **8**, prepared by slow concentration of a

benzene solution of the cyclophane. In the crystal form, **8** contains a disordered furan moiety (Figure 2). Both disordered rings C(4)C(5)C(17)C(18)O(1) and C(4)C(5)C(17′)C(18′)O(1′) were planar within 0.013 Å, and formed angles of 2.3 and 2.7°, respectively, with the plane passing through C(4)C(5)C(7)C(8). The central bond C(4)−C(5) in **8** [1.366(3) Å] was shorter than that in **11**[21] [1.409(4) Å]. It is more correct to describe this structure as a superposition of the two enantiomers (*S*)- and (*R*)-**8** in a 1:1 ratio.

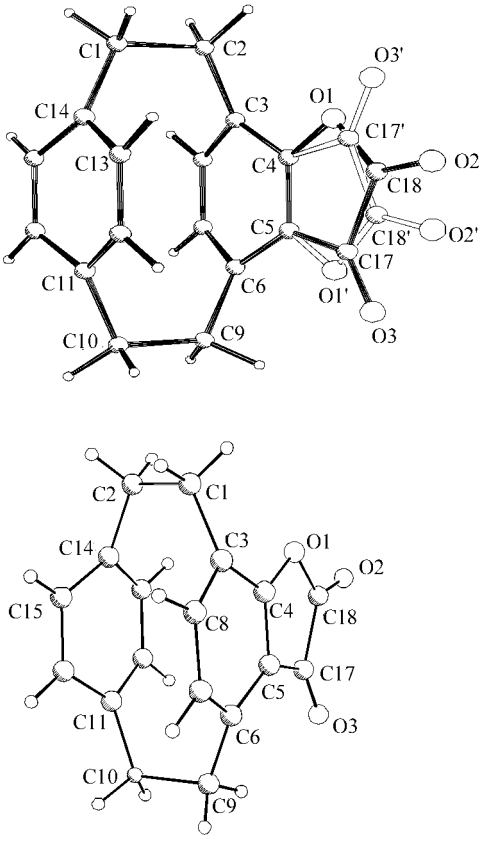


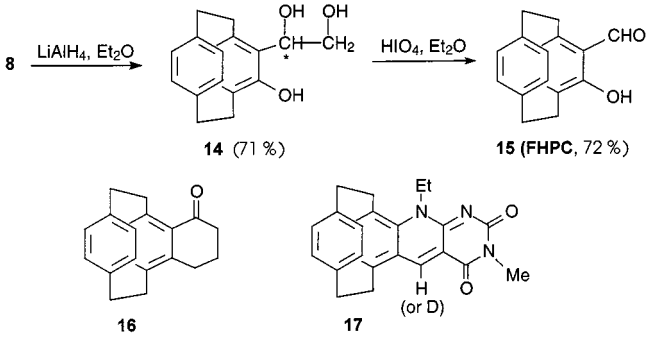
Figure 2. General view of racemic (top) and (*R*)-2,3-dioxo-2,3-dihydrofurano[4,5-*d*][2.2]paracyclophane (**8**, bottom)

X-ray Diffraction Study of Enantiomerically Pure (*R*)-2,3-Dihydro-2,3-dioxofurano[4,5-*d*][2.2]paracyclophane (8)

By starting from (*R*)- and (*S*)-**1** (*ee* > 99%), optically pure (*R*)-**8** ($[\alpha]_D^{25} = -699$, $c = 0.38$, benzene) and (*S*)-**8** ($[\alpha]_D^{25} = +697$, $c = 0.38$, benzene) were also obtained. The single crystal of (*R*)-**8** was prepared by slow concentration of its benzene solution and the result of the X-ray study is shown in Figure 2. The geometric parameters of the [2.2]paracyclophane moiety and the furan ring in (*R*)-**8** are in a good agreement with those obtained for the racemic sample. Thus the furan ring C(4)C(5)C(17)C(18)O(1) is planar within 0.013 Å and forms an angle of 2.5° with the plane passing through C(4)C(5)C(7)C(8). The central bond C(4)−C(5) in (*R*)-**8** is 1.399 Å.

A New Route to FHPC (15)

In the aromatic series, cyclic α-oxo esters analogous to **8** have been reported as precursors for salicylaldehydes.[19b] According to this approach, we carried out the reduction of **8** to the vicinal diol **14** with $LiAlH_4$ in diethyl ether, which took place in 71% yield (Scheme 5). The very low solubility of **8** in diethyl ether required significant amounts of solvent; it thus did not seem very useful to carry out this reaction on a preparative scale. Reduction of **8** by $LiAlH_4$ or $NaBH_4$ in tetrahydrofuran was found to occur in slightly lower yield (67 and 60%, respectively). Finally, a modified procedure involving slow extraction of **8** by diethyl ether in a Soxhlet apparatus followed by reduction of the extract with $LiAlH_4$ was developed. Oxidative cleavage of **14** with $Pb(OAc)_4$ gave a complex mixture of several products, from which the target salicylaldehyde **15** (FHPC) was isolated in 12% yield. On the other hand, treatment of **14** with HIO_4 in diethyl ether produced FHPC in good chemical yield (72%, Scheme 5).



Scheme 5

The complete three-step procedure (from **1** to FHPC) presented in Scheme 2 and Scheme 5 was also performed without purification of the intermediates **8** and **14**. The target FHPC was purified by filtration through a short silica gel column with dichloromethane as eluent. The total yield of **15** from **1** amounted to 50%, making this methodology very attractive for the synthesis of preparative amounts of FHPC, as the chemical yield is comparable with that reported earlier,[4b,9,22] but the procedure does not require inert gases, low temperatures, or laborious chromatographic separation. Application of this procedure to enantiomers of **1** would no doubt also enable one to synthesize (*R*)- or (*S*)-FHPC in enantiomerically pure form.

Diastereoselectivity of the Reduction of 8

The reduction of the cyclic α-oxo ester **8** with $LiAlH_4$ in diethyl ether results in the formation of a stereogenic center at the side chain of the [2.2]paracyclophane moiety and proceeds stereoselectively. The diastereomeric diols **14** were separated by preparative chromatography and characterized by their ^1H NMR and MS data. An elemental analysis was also obtained for the major isomer of **14**. Careful examination of the ^1H NMR spectra of the reaction mixtures allowed the ratio of the diastereomers to be determined as

88:12 (or 76% *de*) when $LiAlH_4$ was added to a solution of **8** in diethyl ether and as 94:6 (88% *de*) when the reduction was performed in the Soxhlet apparatus. The best diastereoselectivity (95% *de*) was observed when the reduction was carried out by slow addition of the solution of **8** in diethyl ether to a suspension of $LiAlH_4$ in the same solvent.

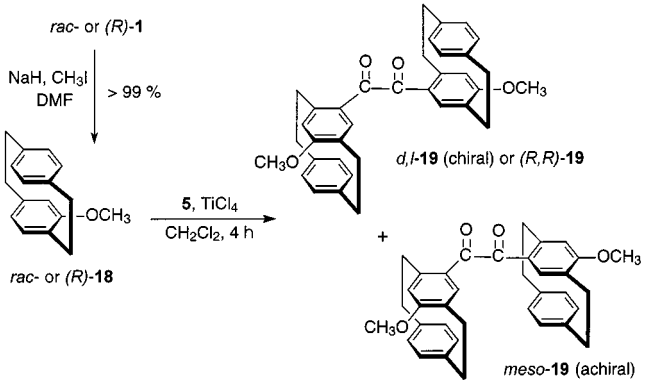
To the best of our knowledge, two other examples of stereoselective reduction of double bonds in rigidly annulated [2.2]paracyclophanes have been reported in the chemical literature[5l] (Scheme 5). The reduction of the C=O group of (1,2,3,4-tetrahydro-4-oxobenzo)[*d*][2.2]paracyclophane (**16**) with $LiAlH_4$ produces *endo*- and *exo*-carbinols in preparative yields of 54 and 27%, respectively.[2] Predominant formation of the carbinol in which the hydroxy group is pointing towards the unsubstituted [2.2]paracyclophane ring (*endo*) indicates that incorporation of hydrogen had occurred preferentially from the unshielded face of the carbonyl group. The reduction of the C=C bond of the polyheterocyclic compound **17** with $NaBD_4$ (or of deuterated **17** with $NaBH_4$) was completely stereoselective.[5a] Analysis of the products obtained, together with the X-ray crystal structure data of **17**, showed that one face of the cycle was completely blocked by an aromatic proton of the unsubstituted aromatic ring of the [2.2]paracyclophane, forcing D or H to enter the system exclusively from the unshielded face of the double bond.

For the diastereoisomers of **14**, the relative configurations of the new asymmetric centers were determined on the basis of their ^1H NMR spectra (including NOESY measurements) supported by AM1 calculations. The X-ray data obtained for the substrate **8** were also taken into account. Thus, AM1-calculated structures demonstrated that the most stable conformation of the conformationally labile side chain in both diastereoisomers (*R**,*R**)- and (*R**,*S**)-**14** was the one with the hydroxymethyl group turned away from the unsubstituted paracyclophane ring. However, in (*R**,*R**)-**14** the formation of an intramolecular hydrogen bond was facile, whereas in (*R**,*S**)-**14**, hydrogen bonding could provoke severe nonbonded interactions between the CH_2OH group and 9-H^A, 10-H^A, or 12-H of the [2.2]paracyclophanyl moiety. According to the X-ray data of **8**, the plane of the furan ring is twisted by only 2° with respect to the plane of the substituted [2.2]paracyclophane ring, making them almost coplanar (Figure 2). It is obvious from the structure that one side of the five-membered ring of **8** is strongly shielded by the protons of the unsubstituted ring of [2.2]paracyclophane. The incoming hydrogen atom can therefore easily approach from the unshielded face of the five-membered ring, resulting in formation of (*R**,*R**)-**14**.

In the 2D NMR spectra of the major isomer of **14** in [D_6]acetone, noticeable NOEs of protons 9-H^A, 10-H^A, and 12-H with α-H were observed. Additionally, the phenolic OH group in the ^1H NMR spectrum of this isomer was registered as a singlet at δ = 9.70 whilst the signals of the OH group bonded to the chiral center were detected as a sharp doublet at δ = 5.69. The spin-spin coupling with α-H (δ = 5.10, ^2J = 6.2 Hz) indicates no fast OH proton exchange (on the NMR timescale); thus a strong intramolecular hydrogen bond between the phenolic and the carbinol OH groups must be formed here. In the spectrum of the minor isomer of **14** in $CDCl_3$, we observed the signal of the phenolic OH group at δ = 7.70−7.90 as a broad singlet whilst no signals were detected for the carbinol OH groups; we interpret this as the absence of hydrogen bonding. Taken together, the ^1H NMR spectroscopic data strongly support the notion that the configuration of the major isomer of **14** is (*R**,*R**) − as expected − and that the minor isomer has the (*R**,*S**) configuration.

Regioselective Oxaloylation of 4-Methoxy[2.2]paracyclophane (18)

In our previous paper dealing with the Friedel−Crafts acylation of 4-hydroxy[2.2]paracyclophane,[6] we reported that the high regioselectivity of the acylation of **1** could be explained by the formation of an intermediate complex of Ti^{IV} with substrate **1** and RC(O)Cl, and that this complex played the key role in determining the regioselectivity of the process. We demonstrated that the replacement of the hydroxy group by a methoxy substituent had a dramatic influence on the regioselectivity of the reaction, and that acylation resulted exclusively in the *para* product. In this work we also investigated the attack of oxalyl chloride on 4-methoxy[2.2]paracyclophane (**18**). The synthesis of this derivative was improved by the use of NaH in DMF (instead of K_2CO_3 in acetone[23]), allowing **18** to be prepared in quantitative yield. Treatment of **18** with 1 equiv. of oxalyl chloride under standard conditions (CH_2Cl_2, 1.3 equiv. $TiCl_4$, room temperature) proceeded *para* regioselectively − as expected − and produced the dimeric α-diketone **19** as the sole product in 89% yield (Scheme 6).



Scheme 6

No traces of *ortho*-substituted or monofunctionalized products were detected in the reaction mixture. The participation of both oxalyl chloride acyl chloride moieties and formation of α-diketones is often observed in Friedel−Crafts oxaloylation of active substrates (such as anisole). However, the difference in the oxaloylation of **18** as compared to simple anisole derivatives lies in the lack of competition between *ortho* and *para* substitution. The exclusive *para* regioselectivity can be explained not only by the impossibility of the formation of the intermediate Ti^{IV}/

substrate/reagent complex, but also by significant steric hindrance in the position *ortho* to the methoxy group.

Diketone **19**, constructed from two chiral [2.2]paracyclophanyl moieties, might in principle be obtained as a mixture of two diastereomers, namely (*R**,*R**)-**19** and *meso*-**19**. According to ^{1}H NMR spectral analysis of the reaction mixture, the ratio of the two diastereomers amounted to 1.3:1. A single crystallization of the mixture from benzene gave the major isomer in 27% yield. We also carried out the oxaloylation of enantiomerically pure (*R*)-**18**, which was in turn synthesized from the corresponding (*R*)-**1** by our new methoxylation procedure. The relative configurations of the diastereomers of **19** were established by ^{1}H NMR spectroscopy, by adding $CDCl_3$ solutions of the diastereomerically pure (*R*,*R*)-**19** to a solution of (*R**,*R**)- and *meso*-**19**. Thus we found that acylation of racemic **18** occurred with a small diastereoselectivity favoring the chiral diastereomer of α-diketone **19** described above.

Conclusion

We have developed a new and effective resolution technique for 4-hydroxy[2.2]paracyclophane (**1**) through its diastereomeric esters with (1*S*)-(−)-camphanic acid, allowing both (*R*)- and (*S*)-**1** to be prepared in very high optical purity. We have demonstrated that the Friedel−Crafts oxaloylation of 4-hydroxy- and 4-methoxy[2.2]paracyclophane (**1** and **18**) in the presence of $TiCl_4$ conforms with the chemical behavior of other recently studied cyclophane derivatives.[6] Thus, treatment of phenol **1** with oxalyl chloride produces the *ortho*-substituted compound **8**, whereas the phenolic methyl ether **18** reacts with formation of the *para*-substituted α-diketone **19**.

Furthermore, a new simple method for the synthesis of 5-formyl-4-hydroxy[2.2]paracyclophane (**15**, FHPC), an efficient chiral inductor molecule, has been found. It has also been determined that the reduction of the carbonyl group of the rigid five-membered ring of 2,3-dihydro-2,3-dioxofurano[4,5-*d*][2.2]paracyclophane (**8**) with $LiAlH_4$ occurs stereoselectively, with up to 95% diastereoselectivity.

Experimental Section

General: Pyridine was distilled twice from KOH. DMF was distilled under reduced pressure from P_2O_5 and stored over molecular sieves (3 Å). Ethyl acetate was washed with saturated aq. K_2CO_3, dried with $CaCl_2$, and distilled from anhydrous K_2CO_3. Dichloromethane was washed successively with conc. H_2SO_4, water, and saturated aq. Na_2CO_3 solution, dried with $CaCl_2$, and successively distilled from P_2O_5 and CaH_2. Et_2O and THF were distilled from sodium benzophenone ketyl under argon before use. (1*S*)-(−)-Camphanic acid was purchased from Fluka; (1*S*)-(−)-camphanoyl chloride, oxalyl chloride, and $LiAlH_4$ were purchased from Merck and were used without purification. The solution of periodic acid was prepared according to a literature procedure.[24] 4-Hydroxy[2.2]paracyclophane was synthesized according to a literature procedure.[25] NMR: Bruker AMX 400 (400 and 100 MHz, for ^{1}H and ^{13}C, respectively). For ^{1}H NMR spectroscopy the residual proton signals of the deuterated solvents were used as internal standards. MS: KRATOS MS890A (70 eV). IR: SPECORD M 82. Optical rotations: EPO-1 in a thermostated cell at 20 or 22 °C. TLC: Silica gel precoated plates "Silufol UV-254" (Chemapol). Column chromatography: Kieselgel 60 (Merck). Enantiomeric analysis of 4-hydroxy[2.2]paracyclophane was performed by HPLC on heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin (50% on OV1701, w/w) at 185 °C with H_2 (0.5 bar) or by GC (Perkin−Elmer Sigma 2000 instrument) on Chiraldex-β-DM (30 m × 0.25 mm) at 180 °C with He as carrier gas.

Synthesis and Resolution of the Diastereomeric Mixture of 3: (1*S*)-(−)-Camphanoyl chloride (**4**, 2.410 g, 11 mmol) was added to a solution of racemic 4-hydroxy[2.2]paracyclophane (**1**, 2.240 g, 10 mmol) in pyridine (25 mL). The mixture was stirred at room temp. for 1 h, diluted with 200 mL of H_2O, and vigorously stirred until a white precipitate was obtained. The precipitate was removed by filtration, washed with H_2O (5 × 100 mL) and pentane (2 × 40 mL), and dried in vacuo to yield 3.800 g (95%) of the mixture of diastereomeric esters **3**. This material was recrystallized from 90 mL of ethyl acetate to give 0.560 g (14%) of (R_p,1*S*)-**3** as a first crop (*de* > 95% according to ^{1}H NMR analysis). From the mother liquor, 0.411 g (11%) of (S_p,1*S*)-**3** was precipitated as a second crop (*de* > 91% according to ^{1}H NMR analysis). The mother liquor was concentrated and the above procedure was repeated twice, using a proportional amount of the solvent each time. Combined fractions enriched in (R_p,1*S*)-**3** (1.150 g) were recrystallized from ethyl acetate to yield 0.780 g (19.4%) of the diastereomer with *de* 97%. Further crystallization from the same solvent gave 0.560 g (14%) of analytically pure material, m.p. 214.0−214.5 °C. $[\alpha]_D^{25} = -24.14$ (c = 0.35, CH_2Cl_2). ^{1}H NMR (C_6D_6): δ = 0.83 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 1.38 (m, 2 H), 1.96 (m, 1 H), 2.28 (m, 1 H), 2.49 (m, 1 H), 2.63−2.83 (m, 4 H), 2.93 (m, 1 H), 3.08−3.27 (m, 2 H), 6.14 (s, 1 H, 5-H, aromatic H), 6.25−6.42 (m, 5 H, aromatic H), 7.16 (dd, ^3J = 8.0, ^4J = 2.0 Hz, 1 H, 12-H, aromatic H). MS (70 eV): *m*/*z* (%) = 404 [M$^+$] (33), 300 (72), 224 (27), 125 (48), 104 (100). $C_{26}H_{28}O_4$ (404.50): calcd. C 77.20, H 6.98; found C 77.42, H 7.17. Combined fractions enriched in (S_p,1*S*)-**3** (1.221 g) were recrystallized from ethyl acetate to yield 0.772 g (19%) of analytically pure material, m.p. 221−222 °C. $[\alpha]_D^{25} = +24.78$ (c = 0.38, CH_2Cl_2). ^{1}H NMR (C_6D_6): δ = 0.80 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.39 (m, 2 H), 1.92 (m, 1 H), 2.23 (m, 1 H), 2.51 (m, 1 H), 2.64−2.83 (m, 4 H), 2.94 (m, 1 H), 3.13−3.30 (m, 2 H), 6.12 (s, 1 H, 5-H, aromatic H), 6.28−6.40 (m, 5 H, aromatic H), 7.18 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, 12-H, aromatic H). MS (70 eV): *m*/*z* (%) = 404 [M$^+$] (28), 300 (63), 224 (21), 125 (45), 104 (100). $C_{26}H_{28}O_4$ (404.50): calcd. C 77.20, H 6.98; found C 77.38, H 7.29. All filtrates were combined and after solvent removal 1.750 g of an equimolar mixture of (R_p,1*S*)-**3** and (S_p,1*S*)-**3** was obtained, which could be used in the resolution again.

(*R*)-4-Hydroxy[2.2]paracyclophane [(*R*)-1]: $LiAlH_4$ (0.450 g, 11.7 mmol) and anhydrous THF (40 mL) were placed in a flask equipped with a Soxhlet apparatus charged with (R_p,1*S*)-**3** (0.474 g, 1.17 mmol). The mixture was heated under reflux for 4 h and, after complete dissolution of (R_p,1*S*)-**3**, further refluxed for 8 h. The mixture was cooled to 0 °C and ethyl acetate (10 mL), H_2O (10 mL), and 2 N HCl (50 mL) were successively added. The reaction mixture was extracted with Et_2O and the combined organic layers were washed with H_2O (2 × 50 mL) and $NaHCO_3$ solution and dried with Na_2SO_4. The solvent was removed in vacuo. The crude mixture was purified by silica gel chromatography (eluent CH_2Cl_2) to yield 0.240 g (92%) of (*R*)-4-hydroxy[2.2]paracyclo-

phane (**1**), m.p. 232.5−234.5 °C (ref.[9,10] m.p. 232−234 °C). *ee* > 99% by GC analysis.

(*S*)-4-Hydroxy[2.2]paracyclophane [(*S*)-1]: This was obtained by the same method from (S_p,1*S*)-**3** (0.451 g, 1.11 mmol) in 94% chemical yield (0.233 g); m.p. 229−230 °C (ref.[4g] m.p. 225 °C, ref.[10] m.p. 232−234 °). *ee* > 99% by GC analysis.

Oxaloylation of Racemic 4-Hydroxy[2.2]paracyclophane (1) in the Presence of $AlCl_3$: A solution of **1** (0.200 g, 0.9 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C to a red suspension of $AlCl_3$ (0.156 g, 1.18 mmol) in CH_2Cl_2 (3 mL). The orange suspension was stirred for 15 min at 0 °C, and oxalyl chloride (**5**, 0.078 mL, 0.114 g, 0.9 mmol) was then added. The resulting dark brown solution was stirred at room temp. for 48 h. The reaction mixture was poured into ice water and vigorously stirred for 10 min. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), Et_2O (2 × 15 mL), and the organic layers were washed with H_2O (2 × 15 mL), $NaHCO_3$ solution, and water. The combined organic solutions were dried with Na_2SO_4 and the solvent was evaporated in vacuo. The solid residue (0.160 g) was separated on silica gel with CH_2Cl_2 and CH_2Cl_2/MeOH (5:2). From the combined fractions with R_f = 0.5 (CH_2Cl_2), starting material **1** (0.074 g, 47%) was isolated. From the combined fractions with R_f = 0.21 (CH_2Cl_2), ethyl (4-hydroxy[2.2]paracyclophan-7-yl)glyoxylate (**7**, 0.019 g, 6.5%) was obtained as a colorless oil. IR (neat): $\tilde{\nu}$ = 1723 cm^{-1} (C-18=O), 1655 (C-17=O). ^1H NMR ($CDCl_3$): δ = 1.40 (t, 3 H, $-CH_2CH_3$), 2.65 (m, 2 H, $-CH_2CH_2-$), 3.00−3.20 (m, 4 H, $-CH_2CH_2-$), 3.35 (m, 1 H, $-CH_2CH_2-$), 4.05 (m, 1 H, $-CH_2CH_2-$), 4.45 (m, 2 H, $-CH_2CH_3$), 5.00 (s, 1 H, aromatic H), 5.40 (br. s, 1 H, -OH), 6.30 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, aromatic H), 6.45 (d, ^3J = 7.8 Hz, 1 H, aromatic H), 6.72 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, aromatic H), 6.85 (d, ^3J = 7.8 Hz, 1 H, aromatic H), 7.10 (s, 1 H, aromatic H). MS (70 eV): *m*/*z* (%) = 324 [M^+], 306 (16), 252 (46), 251 (77), 233 (18), 220 (80), 192 (83), 164 (80), 147 (94), 119 (50), 104 (100). From the combined fractions with R_f = 0.20 (CH_2Cl_2/MeOH, 5:2), (4-hydroxy[2.2]paracyclophan-5-yl)glyoxylic acid (**6**, 0.043 g, 16%) was obtained as a yellow powder, m.p. 190 °C (decomp.). IR (nujol): $\tilde{\nu}$ = 1617 cm^{-1} (C-18=O), 1577 (C-17=O). ^1H NMR ([D$_6$]DMSO): δ = 2.80 (m, 1 H, $-CH_2CH_2-$), 2.70 (m, 1 H, $-CH_2CH_2-$), 2.90−3.16 (m, 4 H, $-CH_2CH_2-$), 3.35 (m, 2 H, $-CH_2CH_2-$), 6.13 (d, ^3J = 7.8 Hz, 1 H, aromatic H), 6.35−6.50 (m, 3 H, aromatic H), 6.58 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, aromatic H), 6.75 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, aromatic H). ^{13}C NMR ($CDCl_3$): δ = 29.83, 33.45, 34.24, 34.84 (C-1, -2, -9, -10), 123.64, 127.65, 138.56, 139.40, 143.18 (C-3, -5, -6, -11, -14), 125.18, 127.53, 130.97, 132.44, 132.92, 138.09, (C-7, -8, -12, -13, -15, -16), 159.14 (C-4), 169.92 (C-18=O), 198.79 (C-17=O). MS (70 eV): *m*/*z* (%) = 278 (12) [$M^+ - H_2O$], 250 (25), 146 (5), 104 (100). $C_{18}H_{16}O_2 \cdot H_2O$ (314.20): calcd. C 68.81, H 5.73; found C 68.98, H 5.60.

Oxaloylation of Racemic 4-Hydroxy[2.2]paracyclophane (1) in the Presence of $TiCl_4$: $TiCl_4$ (0.176 mL, 0.300 g, 1.6 mmol) and oxalyl chloride (0.16 mL, 0.180 g, 1.4 mmol) were successively added at 0 °C to a solution of **1** (0.250 g, 1.12 mmol) in CH_2Cl_2 (12.5 mL), and the resulting dark cherry-colored solution was stirred at room temp. for 1 h. The reaction mixture was poured into ice/water and vigorously stirred for 10 min. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), the orange organic layer was washed with H_2O (2 × 15 mL), $NaHCO_3$ solution, and H_2O, and dried with Na_2SO_4, and the solvent was evaporated in vacuo to yield 0.307 g (99%) of 2,3-dihydro-2,3-dioxofurano[4,5-*d*][2.2]paracyclophane (**8**). An analytically pure sample of **8** was prepared by crystallization from heptane, m.p. 174−176 °C. IR (vaseline): $\tilde{\nu}$ = 1822 cm^{-1} (C-18=O), 1727 (C-17=O). ^1H NMR ($CDCl_3$): δ = 2.80 (m, 1 H, $-CH_2CH_2-$), 2.92 (m, 1 H, $-CH_2CH_2-$), 3.06−3.26 (m, 4 H, $-CH_2CH_2-$), 3.40 (m, 1 H, $-CH_2CH_2-$), 3.90 (m, 1 H, $-CH_2CH_2-$), 6.37 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, aromatic H), 6.48 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, aromatic H), 6.60 (d, ^3J = 7.8 Hz, 1 H, aromatic H), 6.70 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, aromatic H), 6.81 (d, ^3J = 7.8 Hz, 1 H, aromatic H), 6.84 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1 H, aromatic H). ^{13}C NMR ($CDCl_3$): δ = 28.92, 31.17, 33.27, 33.80 (C-1, -2, -9,-10), 121.27, 124.94, 138.73, 140.12, 144.38 (C-3, -5, -6, -11, -14), 127.67, 129.78, 131.41, 133.61, 134.19, 145.36 (C-7, -8, -12, -13, -15, -16), 156.39 (C-4), 161.98 (C-18=O), 178.13 (C-17=O). MS (70 eV): *m*/*z* (%) = 278 (30) [M^+], 251 (14), 146 (10), 104 (100). $C_{18}H_{14}O_3$ (278.29) calcd. C 77.68, H 5.07; found C 77.65, H 5.00.

Oxaloylation of (*R*)-4-Hydroxy[2.2]paracyclophane [(*R*)-1]: The synthesis was carried out as described for the racemic compound, starting from (*R*)-**1** (0.058 g, 0.26 mmol), $TiCl_4$ (0.037 mL, 0.064 g, 0.34 mmol), and oxalyl chloride (0.022 mL, 0.033 g, 0.26 mmol), to yield 0.069 g (96%) of (*R*)-**8**. An analytically pure sample was prepared by crystallization from heptane (0.038 g, 53%), m.p. 181.2−182.5 °C. $[\alpha]_D^{22}$ = −699 (*c* = 0.4, C_6H_6). $C_{18}H_{14}O_3$ (278.29) calcd. C 77.68, H 5.07; found C 78.04, H 4.95.

Oxaloylation of (*S*)-4-Hydroxy[2.2]paracyclophane [(*S*)-1]: The synthesis was carried out as described for the racemic compound, starting from (*S*)-**1** (0.084 g, 0.38 mmol), $TiCl_4$ (0.05 mL, 0.093 g, 0.49 mmol), and oxalyl chloride (0.032 mL, 0.048 g, 0.38 mmol), to yield 0.100 g (96%) of (*S*)-**8**. An analytically pure sample was prepared by crystallization from heptane (0.058 g, 56%), m.p. 181.2−182.5 °C. $[\alpha]_D^{22}$ = +697 (*c* = 0.4, C_6H_6). $C_{18}H_{14}O_3$ (278.29) calcd. C 77.68, H 5.07; found C 77.66, H 5.18.

(4-Hydroxy[2.2]paracyclophan-5-yl)glyoxylic Acid (6): A solution of **8** (0.145 g, 0.5 mmol) in a 1:1 mixture of CH_2Cl_2/$CHCl_3$ (5 mL) was placed on silica gel and washed with 200 mL of CH_2Cl_2 until the orange-colored zone stopped moving through the column. The solvent was changed to methanol, allowing the collection of the yellow compound with R_f < 0.1 (CH_2Cl_2). This was additionally purified by silica gel chromatography with C_6H_6/MeOH (4:1), to give 0.125 g (81%) of (4-hydroxy[2.2]paracyclophan-5-yl)glyoxylic acid (**6**).

Oxaloylation of 2-Isopropyl-5-methylphenol with $TiCl_4$: $TiCl_4$ (0.48 mL, 0.830 g, 4.34 mmol) and oxalyl chloride (0.3 mL, 0.430 g, 3.34 mmol) were successively added at 0 °C to a solution of thymol (0.500 g, 3.34 mmol) in CH_2Cl_2 (20 mL), and the resulting dark red solution was stirred at room temp. for 48 h. The reaction mixture was poured into ice/water and was vigorously stirred for 10 min. The mixture was extracted with CH_2Cl_2 (4 × 20 mL), the yellow organic layer was washed with H_2O (2 × 15 mL), $NaHCO_3$ solution, and water, and dried with Na_2SO_4, and the solvent was evaporated in vacuo to give 0.590 g of the crude product as a yellow oil. The mixture was separated on silica gel with CH_2Cl_2 as the eluent. From the fractions with R_f = 0.50 (CH_2Cl_2), the starting thymol (0.385 g, 77%) was isolated. From the combined fractions with R_f = 0.63 (CH_2Cl_2/MeOH, 20:1), bis(4-hydroxy-5-isopropyl-2-methylphenyl) diketone (0.011 g, 3%) was collected. ^1H NMR ($CDCl_3$): δ = 1.15 (d, 6 H, $-CHCH_3$), 2.40 (s, 3 H, $-CH_3$), 3.15 (m, 1 H, $-CHCH_3$), 5.25 (br. s, 1 H, −OH), 6.62 (s, 1 H, aromatic H), 7.19 (s, 1 H, aromatic H). MS (70 eV): *m*/*z* (%) = 326 (33) [M^+], 311 (100), 295 (25), 283 (86), 269 (38), 268 (45). From the combined fractions with R_f = 0.22 (CH_2Cl_2/MeOH, 20:1), (2-hydroxy-3-isopropyl-6-methylphenyl)oxoacetic acid (0.117 g, 16%) was collected. ^1H NMR ([D$_6$]DMSO): δ = 1.16 (d, 6 H, $-CHCH_3$), 2.15 (s, 3 H, $-CH_3$), 3.15 (m, 1 H, $-CHCH_3$), 6.55 (d,

1 H, aromatic H), 7.05 (d, 1 H, aromatic H), 13.90 (s, 1 H, −OH). MS (70 eV): *m/z* (%) = 204 (3) [$M^+ - H_2O$], 176 (87), 161 (89), 149 (37), 148 (100), 133 (50), 120 (31).

***O*-Acylation of 4-Hydroxy[2.2]paracyclophane (1) with Oxalyl Chloride (5):** Compound **1** (0.150 g, 0.67 mmol) was added in portions to a solution of oxalyl chloride (**5**, 0.076 mL, 0.085 g, 0.67 mmol) and 4-(dimethylamino)pyridine (0.160 g, 1.34 mmol) in CH_2Cl_2 (9 mL), and the mixture was stirred for 0.5 h at room temp. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel with CH_2Cl_2 as eluent to produce 0.150 g (89%) of dimer **13**. An analytically pure sample of **13** (0.090 g, 82%) was obtained as a white powder by two successive crystallizations from C_6H_6, m.p. 242.5−244.5 °C. IR (KBr): $\tilde{\nu}$ = 3448 cm^{-1} (−OC(O), 2950 (−OAr), 1740 (C-17,17′=O). ^1H NMR ($CDCl_3$): δ = 2.85 (m, 2 H, $-CH_2CH_2-$), 3.00−3.25 (m, 12 H, $-CH_2CH_2-$), 2.35 (m, 2 H, $-CH_2CH_2-$), 6.30 (br. s, 2 H, 5-H, 5-H′, aromatic H), 6.47−6.65 (m, 10 H, aromatic H), 7.06 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 2 H, aromatic H). ^{13}C NMR ($CDCl_3$): δ = 32.32, 32.35 (C-2, -2′), 35.07, 35.64, 36.00 (C-1, -1′, -9, -9′, -10, -10′), 131.52, 139.91, 140.14, 142.94 (C-3,- 3′, -6′, -6, -11, -11′, -14, -14′), 149.21 (C-4, -4′), 156.17, 156.25 (C-17, C-17′=O). MS (70 eV): *m/z* (%) = 502 (5) [M^+], 296 (4), 223 (16), 120 (37), 104 (100). $C_{34}H_{30}O_4$ (502.58) calcd. C 81.25, H 6.02; found C 81.31, H 5.80.

Soxhlet Reduction of 2,3-Dihydro-2,3-dioxofurano[4,5-*d*][2.2]paracyclophane (8): $LiAlH_4$ (0.219 g, 5.76 mmol) and anhydrous ether (50 mL) were placed in a flask equipped with a Soxhlet extractor charged with **8** (0.160 g, 0.576 mmol). After this had been heated under reflux for 6 h, all **8** had dissolved; the mixture was then cooled to 0 °C and ethyl acetate (10 mL), H_2O (10 mL), and 2 N HCl (50 mL) were added successively. The mixture was extracted with Et_2O, the combined organic layers were washed with H_2O (2 × 50 mL) and $NaHCO_3$ solution and dried with Na_2SO_4, and the solvent was removed in vacuo to give 0.155 g of crude 5-(1,2-dihydroxyethyl)-4-hydroxy-[2.2]paracyclophane (**14**). As shown by ^1H NMR spectroscopy, the ratio of diastereomeric diols (*R**,*R**)/(*R**,*S**)-**14** was 94:6 (*de* 88%). The mixture was separated by chromatography on silica gel with benzene/ethyl acetate (1:1) as eluent. From the combined fractions with R_f = 0.38 (benzene/ethyl acetate, 1:1), (*R**,*R**)-**14** (0.094 g, 58%) was obtained. $C_{18}H_{20}O_3$ (284.34) calcd. C 76.03, H 7.09; found C 76.04, H 6.82. This fraction was recrystallized from $CHCl_3$ to yield (*R**,*R**)-**14** (0.048 g, 29%) as colorless crystals, m.p. 139−141 °C. ^1H NMR ($CDCl_3$): δ = 2.57 (m, 1 H, $-CH_2CH_2-$), 2.75 (m, 1 H, $-CH_2CH_2-$), 2.95−3.25 (m, 2 H, $-CH_2CH_2-$), 3.38−4.50 (m, 3 H, $-CH_2CH_2-$), 3.42 (dd, ^2J = 11.2, ^3J = 3.7 Hz, 1 H, CH_2), 3.46 (m, 1 H, $-CH_2CH_2-$), 3.52 (dd, ^2J = 11.2, ^3J = 3.7 Hz, 1 H, CH_2), 4.94 (m, 1 H, α-H), 6.16 (d, ^3J = 7.8 Hz, 1 H, aromatic H), 6.38 (d, ^3J = 7.8 Hz, 1 H, aromatic H), 6.43 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, aromatic H), 6.57 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1 H, aromatic H), 6.69 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1 H, aromatic H), 7.01 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1 H, aromatic H), 8.9 (s, 1 H, OH). MS (70 eV): *m/z* (%) = 284 (11) [M^+], 266 (29), 174 (0.39), 162 (40), 147 (7), 144 (30), 134 (75), 104 (79). From the combined fractions with R_f = 0.27 (benzene/ethyl acetate, 1:1), (*R**,*S**)-**14** (0.006 g, 4%) was obtained. ^1H NMR ($CDCl_3$): δ = 2.70 (m, 1 H, $-CH_2CH_2-$), 2.89−3.20 (m, 6 H, $-CH_2CH_2-$), 3.40 (m, 1 H, $-CH_2CH_2-$), 4.15 (d, *J* = 4.7 Hz, 2 H, CH_2), 4.85 (m, 1 H, α-H), 6.16 (d, ^3J = 7.8 Hz, 1 H, aromatic H), 6.37 (d, ^3J = 7.8 Hz, 1 H, aromatic H), 6.39 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, aromatic H), 6.56 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1 H, aromatic H), 6.65 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1 H, aromatic H), 6.81 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1 H, aromatic H), 7.70 (br. s, 1 H, OH). MS (70 eV): *m/z* (%) = 284 (3) [M^+], 266 (8), 264 (15), 252 (40), 161 (14), 145 (10), 144 (29), 104 (100).

Reduction of 2,3-Dihydro-2,3-dioxofurano[4,5-*d*][2.2]paracyclophane (8): $LiAlH_4$ (0.197 g, 5.2 mmol) was added to a solution of crude **8** (0.142 g, 0.52 mmol) in anhydrous Et_2O (50 mL) and the mixture was refluxed for 6 h. The mixture was cooled to 0 °C and ethyl acetate (10 mL), H_2O (10 mL), and 2 N HCl (50 mL) were added successively. The reaction mixture was worked up as described above to provide 0.145 g of crude 5-(1,2-dihydroxyethyl)-4-hydroxy-[2.2]paracyclophane (**14**). The ratio of diastereomeric vicinal diols (*R**,*R**)/(*R**,*S**)-**14** was determined by ^1H NMR spectroscopy as 88:12 (*de* 76%). The mixture was separated on silica gel with benzene/ethyl acetate (1:1) as eluent. From the combined fractions with R_f = 0.27−0.38 (benzene/ethyl acetate, 1:1), a mixture of (*R**,*R**)/(*R**,*S**)-**14** (0.102 g, 70%) was obtained.

Oxidative Cleavage of 5-(1,2-Dihydroxyethyl)-4-hydroxy[2.2]paracyclophane (14) with Periodic Acid: A solution of periodic acid (0.044 g, 0.194 mmol) in Et_2O (2.32 mL) was added to a solution of the diastereomeric (*R**,*R**)/(*R**,*S**)-**14** mixture (88:12, 0.055 g, 0.194 mmol) in Et_2O (2 mL), and the reaction mixture was stirred at room temp. for 1 h until a residue of HIO_3 precipitated as a yellowish powder. The reaction mixture was successively washed with $Na_2S_2O_3$ solution, H_2O, and Na_2CO_3 solution, and dried with Na_2SO_4. The solvent was removed in vacuo and the yellow residue (0.050 g) was purified by chromatography on silica gel with benzene as eluent to yield 0.037 g (72%) of FHPC (**15**).

Synthesis of FHPC (15) on a Preparative Scale: Acylation of **1** (1.020 g, 4.54 mmol) in CH_2Cl_2 (50 mL) with oxalyl chloride (0.53 mL, 0.590 g, 4.7 mmol) and $TiCl_4$ (0.67 mL, 1.159 g, 6.1 mmol) produced after workup 1.250 g (99%) of 2,3-dihydro-2,3-dioxofurano[4,5-*d*][2.2]paracyclophane (**8**). Without purification, this was reduced with $LiAlH_4$ (1.730 g, 45.4 mmol) in dry Et_2O (250 mL) to yield 1.230 g of crude 5-(1,2-dihydroxyethyl)-4-hydroxy[2.2]paracyclophane (**14**), which was dissolved in Et_2O (30 mL) and oxidized with a periodic acid solution in Et_2O (72 mL, 1.370 g, 4.6 mmol). After workup, the yellow solid (ca. 1 g) was purified on a short column (SiO_2, eluent CH_2Cl_2) to provide 0.570 g (50%) of pure **15** and 0.370 g of a mixture of unidentified products.

4-Methoxy[2.2]paracyclophane (18): NaH (0.010 g, 0.24 mmol) was added to a solution of **1** (0.050 g, 0.22 mmol) in DMF (1 mL), the resulting brown solution was stirred at room temp. for 1 h, and MeI (0.021 mL, 0.047 g, 0.33 mmol) was added. The reaction mixture was stirred for an additional 2 h, diluted with H_2O (10 mL), extracted with Et_2O (5 × 20 mL), and dried with Na_2SO_4. After evaporation of the solvent, the solid residue was purified by column chromatography on silica gel (eluent C_6H_6) to furnish 0.068 g (94%) of **18**. Crystallization from EtOH yielded 0.049 g (68%) of **18**, m.p. 114−115.5 °C (ref.[23] m.p. 116−117 °C).

(*R*)-4-Methoxy[2.2]paracyclophane [(*R*)-18]: This was prepared by treatment of (*R*)-**1** (0.070 g, 0.3 mmol) in DMF (1.5 mL) with NaH (0.013 g, 0.33 mmol) and MeI (0.028 mL, 0.064 g, 0.45 mmol), to give 0.072 g (98%) of (*R*)-**18**. An analytically pure sample was obtained by crystallization from EtOH (0.037 g, 50%), m.p. 126.5−128.0 °C (ref.[23] m.p. 116−117° C, for racemic **18**). $[\alpha]_D^{20}$ = −19.23 (*c* = 0.52, $CHCl_3$). The ^1H NMR spectroscopic data agreed with those of the of racemic sample. $C_{17}H_{18}O$ (238.20): calcd. C 85.72, H 7.61; found C 85.75, H 7.57.

Oxaloylation of 4-Methoxy[2.2]paracyclophane (18): $TiCl_4$ (0.06 mL, 0.110 g, 0.56 mmol) and oxalyl chloride (0.049 mL, 0.055 g, 0.43 mmol) were added to a solution of 4-methoxy[2.2]-

paracyclophane (**18**, 0.100 g, 0.43 mmol) in CH_2Cl_2 (4.5 mL), cooled to 0 °C, and the resulting dark violet solution was stirred at room temp. for 1 h. The reaction mixture was poured into a mixture of 2 N HCl and ice and vigorously stirred for 0.5 h. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were successively washed with H_2O (2 × 50 mL), $NaHCO_3$ solution, and H_2O, and dried with Na_2SO_4. After solvent removal in vacuo, 0.129 g (98%) of **19** was obtained as a mixture of two diastereomers in 1:1.3 ratio (^{1}H NMR analysis). Recrystallization from benzene/heptane (1:1.5) yielded 0.030 g (27%) of (*R**,*R**)-**19**, m.p. 263−265 °C. IR (KBr): $\tilde{\nu}$ = 3340 cm^{-1} (−OCH_3) 2927, 2850 (−OAr), 1647 (17-C=O). ^{1}H NMR ($CDCl_3$): δ = 2.48 (m, 2 H), 2.82 (m, 2 H), 2.93−3.34 (m, 10 H), 3.78 (s, 6 H, OCH_3), 4.21 (m, 2 H), 5.80 (s, 2 H, 5-H, 5′-H, aromatic H), 6.48 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 2 H, aromatic H), 6.54 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 2 H, aromatic H), 6.70 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 2 H, aromatic H), 6.79 (s, 2 H, 8-H, 8′-H, aromatic H), 6.85 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 2 H, aromatic H). ^{13}C NMR ($CDCl_3$): δ = 31.28, 33.46, 34.81, 35.46 (C-1, -2, -9, -10), 54.78 (OCH_3), 127.12, 127.39, 139.04, 139.71, (C-3, -6, -11, -14), 120.17, 128.29, 130.91, 133.06, 133.22, 139.98 (C-5, -8, -12, -13, -15, -16), 147.87 (C-7), 161.71 (C-4), 195.44 (C=O). MS (70 eV): *m*/*z* (%) = 530 (3) [M^+], 266 (39), 265 (100), 161 (75), 104 (14). $C_{36}H_{34}O_4$ (530.20) calcd. C 81.48, H 6.46; found C 81.76, H 6.59. From the combined filtrates, the chemical shifts for (*R**,*S**)-**19** were determined: ^{1}H NMR ($CDCl_3$): δ = 2.50 (m, 2 H), 2.80 (m, 2 H), 2.95−3.42 (m, 10 H), 3.80 (s, 6 H, OCH_3), 4.39 (m, 2 H), 5.77 (s, 2 H, 5-H, 5′-H, aromatic H), 6.35 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 2 H, aromatic H), 6.54 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 2 H, aromatic H), 6.70−6.74 (m, 4 H, ^3J = 7.8, ^4J = 1.7 Hz, aromatic H), 6.95 (s, 2H, 8-H, 8′-H, aromatic H).

Oxaloylation of (*R*)-18: This was performed as described above for racemic **18**, starting from (*R*)-**18** (0.037 g, 0.155 mmol), $TiCl_4$ (0.022 mL, 0.038 g, 0.20 mmol), and oxalyl chloride (0.013 mL, 0.020 g, 0.155 mmol) to yield 0.039 g (95%) of (*R*,*R*)-**19**, m.p. 244−245.5 °C. $[\alpha]_D^{20}$ = +125.0 (*c* = 0.48, $CHCl_3$). ^{1}H NMR

Table 1. Summary of the crystal data, data collection, and refinement parameters for the four crystal structures reported in this paper

Compound	(R_p,1*S*)-**3**	(S_p,1*S*)-**3**	*rac*-**8**	(*S*)-**8**
Empirical formula	$C_{26}H_{28}O_4$	$C_{26}H_{28}O_4$	$C_{18}H_{14}O_3$	$C_{18}H_{14}O_3$
M_r	404.48	404.48	278.29	278.29
Crystal habit	colorless prism	colorless plate	orange prism	orange prism
Crystal size [mm]	0.3 × 0.1 × 0.1	0.6 × 0.3 × 0.2	0.4 × 0.4 × 0.8	0.3 × 0.3 × 0.1
Crystal system	orthorhombic	monoclinic	monoclinic	orthorhombic
Space group	$P2_12_12_1$	$P2_1$	$P2_1/n$	$P2_12_12_1$
Cell constants:				
a [Å]	13.1342(6)	7.541(5)	7.829(2)	7.746(1)
b [Å]	13.4024(6)	11.269(2)	18.055(4)	9.271(2)
c [Å]	23.581(1)	12.815(2)	9.289(2)	18.111(3)
β [°]	−	91.54(4)	90.585(5)	−
V [Å^3]	4151.0(3)	1088.6(7)	1313.0(5)	1300.5(4)
Z	8	2	4	4
$D_{calcd.}$ [g cm^{-3}]	1.294	1.234	1.408	1.421
Diffractometer	Bruker SMART	CAD4 Enraf−Nonius	Bruker SMART	Bruker SMART
T [K]	110(2)	293(2)	220(2)	110(2)
Radiation	Mo-K_α (λ = 0.71073)	Mo-K_α (λ = 0.71073)	Mo-K_α (λ = 0.71073)	Mo-K_α (λ = 0.71073)
Scans mode	and ω	θ − 5/3θ	and ω	and ω
$2\theta_{max}$, deg	63.46	49.94	60.38	60.00
Abs.coeff., μ(Mo-K_α), cm^{-1}	0.86	0.82	0.95	0.96
Absorption correction	none	none	none	none
Structure solution	direct method	direct method	direct method	direct method
Refinement method	full-matrix, least squares on F^2	full-matrix, least squares on F^2	full-matrix, least squares on F^2	full-matrix, least squares on F^2
No. of reflections collect	54172	2257	19678	10099
No. of independent reflections	13085 (*R*int = 0.0904)	2016 (*R*int = 0.0956)	3826 (*R*int = 0.0544)	3768 (*R*int = 0.0622)
No. of reflections used in refinement	13085	1995	3797	3768
No. of observed reflections [$I > 2\sigma(I)$]	11601	1620	2110	3201
Absolute structure parameter	0.12(49)	1.22(243)	−	−0.4(10)
No. of parameters	765	271	291	246
R_1 (on *F* for obsd. refls)[a]	0.0492	0.0577	0.0667	0.0542
wR_2 (on F^2 for all refl.)[b]	0.1253	0.1806	0.2215	0.1347
Weighting scheme	$w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ $P = 1/3(F_o^2 + 2F_c^2)$	$w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ $P = 1/3(F_o^2 + 2F_c^2)$	$w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ $P = 1/3(F_o^2 + 2F_c^2)$	$w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ $P = 1/3(F_o^2 + 2F_c^2)$
a	0.1000	0.1340	0.1000	0.1000
b	0.0000	0.0371	0.0000	0.0000
F(000)	1744	432	584	584
GOOF	0.915	1.030	1.097	0.978
Largest diff. peak and hole [eÅ^{-3}]	0.460 and −0.238	0.231 and −0.218	0.224 and −0.158	0.431 and −0.265
Deposition number CCDC-	-165489	-165329	-165328	-165327

[a] $R_1 = \Sigma||F_o| - |F||/\Sigma(F_o)$ for observed reflections. [b] $wR_2 = \{\Sigma[w(F^2_o - F^2_c)^2/\Sigma[w(F^2_o)^2]\}^{0.5}$ for all reflections.

($CDCl_3$), δ = 2.48 (m, 2 H), 2.82 (m, 2 H), 2.93−3.34 (m, 10 H), 3.80 (s, 6 H, OCH_3), 4.41 (m, 2 H), 5.80 (s, 2 H, 5-H, 5′-H, aromatic H), 6.49 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, aromatic H), 6.54 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 1 H, aromatic H), 6.70 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 2 H, aromatic H), 6.78 (s, 2 H, 8-H, 8′-H, aromatic H), 6.85 (dd, ^3J = 7.8, ^4J = 1.7 Hz, 2 H, aromatic H). $C_{36}H_{34}O_4$ (530.20) calcd. C 81.48, H 6.46; found C 81.38, H 6.57.

X-ray Crystallography: A summary of the crystal data, data collection, and refinement parameters for the four crystal structures reported in this paper is given in Table 1. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publications (see ref. numbers in Table 1). Atomic coordinates, full bond lengths and angles, and thermal parameters are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail deposit@ccdc.cam.ac.uk].

Acknowledgments

Financial support of this work by INCO-COPERNICUS (JC15-CT96-0722), the Russian Science Foundation (00-03-32683a and 00-03-32807a), and the Fonds der Chemischen Industrie is gratefully acknowledged. The authors are grateful to Prof. W. König (Hamburg, Germany) and Prof. V. Davankov and Dr. M. Il'in (Moscow, Russia) for enantiomeric analysis performed for the (*R*)- and (*S*)-4-hydroxy[2.2]paracyclophanes, and to Prof. Yu. N. Belokon' (Moscow, Russia) for helpful discussions.

[1] [1a] D. J. Cram, N. L. Allinger, *J. Am. Chem. Soc.* **1955**, *77*, 6289−6294. [1b] J. L. Marshall, L. Hall, *Tetrahedron* **1981**, *37*, 1271−1275.

[2] H. Falk, P. Reich-Rohrwig, K. Schlögl, *Tetrahedron* **1970**, *26*, 511−527.

[3] D. A. Lightner, D. T. Hefelfinger, T. W. Powers, G. W. Frank, K. N. Trueblood, *J. Am. Chem. Soc.* **1972**, *94*, 3492−3497.

[4] [4a] H. J. Reich, K. E. Yelm, *J. Org. Chem.* **1991**, *56*, 5672−5679. [4b] V. I. Rozenberg, V. G. Kharitonov, D. Yu. Antonov, E. V. Sergeeva, A. A. Aleshkin, N. S. Ikonnikov, S. A. Orlova, Yu. N. Belokon′, *Angew. Chem.* **1994**, *106*, 106−108; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 91−93. [4c] D. Yu. Antonov, Yu. N. Belokon′, N. S. Ikonnikov, S. A. Orlova, A. P. Pisarevsky, N. I. Raevsky, V. I. Rozenberg, E. V. Sergeeva, Yu. T. Struchkov, V. I. Tararov, E. V. Vorontsov, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1873−1879. [4d] E. V. Sergeeva, V. I. Rozenberg, E. V. Vorontsov, T. I. Danilova, Z. A. Starikova, A. I. Yanovsky, Yu. N. Belokon', H. Hopf, *Tetrahedron: Asymmetry* **1996**, *7*, 3445−3454. [4e] P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante, P. J. Reider, *J. Am. Chem. Soc.* **1997**, *119*, 6207−6208. [4f] K. Rossen, P. J. Pye, A. Maliakal, R. P. Volante, *J. Org. Chem.* **1997**, *62*, 6462−6463. [4g] D. Pamperin, C. Schulz, H. Hopf, C. Syldatk, M. Pietzsch, *Eur. J. Org. Chem.* **1998**, 1441−1445. [4h] V. I. Rozenberg, N. V. Dubrovina, E. V. Sergeeva, D. Yu. Antonov, Yu. N. Belokon', *Tetrahedron: Asymmetry* **1998**, *9*, 653−656. [4i] N. V. Vorontsova, V. I. Rozenberg, E. V. Vorontsov, O. L. Tok, Yu. N. Bubnov, *Russ. Chem. Bull.* **2000**, 912−919. [4j] L. Minuti, A. Taticchi, A. Marrocchi, *Tetrahedron: Asymmetry* **2000**, *11*, 4221−4225.

[5] [5a] R. Yanada, Y. Higashikawa, Y. Miwa, T. Taga, F. Yoneda, *Tetrahedron: Asymmetry* **1992**, *3*, 1387−1390. [5b] A. Pelter, R. A. N. C. Crump, H. Kidwell, *Tetrahedron Lett.* **1996**, *37*, 1273−1276. [5c] Yu. Belokon', M. Moskalenko, N. Ikonnikov, L. Yashkina, D. Antonov, E. Vorontsov, V. Rozenberg, *Tetrahedron: Asymmetry* **1997**, *8*, 3245−3250. [5d] A. Pelter, H. Kidwell, R. A. N. C. Crump, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3137−3139. [5e] D. S. Masterson, D. T. Glatzhofer, *J. Mol. Catal. A: Chem.* **2000**, *161*, 65−68. [5f] A. H. Vetter, A. Berkessel, *Tetrahedron Lett.* **1998**, *39*, 1741−1744. [5g] F. Fringuelli, O. Piermatti, F. Pizzo, R. Ruzziconi, *Chem. Lett.* **2000**, 38−39. [5h] X.-L. Hou, X.-W. Wu, L.-X. Dai, B.-X. Cao, J. Sun, *J. Chem. Commun.* **2000**, 1195−1196. [5i] A. Marchand, A. Maxwell, B. Mootoo, A. Pelter, A. Reid, *Tetrahedron* **2000**, *56*, 7331−7338. [5j] C. Bolm, T. Kühn, *Synlett* **2000**, 899−901. [5k] V. I. Rozenberg, D. Y. Antonov, R. P. Zhuravsky, E. V. Vorontsov, V. Khrustalev, Z. A. Starikova, N. S. Ikonnikov, Yu. N. Belokon', *Tetrahedron: Asymmetry* **2000**, *11*, 2683−2693. [5l] For a comprehensive study of the diastereoselectivity of hydride reductions and the addition of metal organic reagents to cyclophane aldehydes and ketones see: T. Laue, Ph.D. dissertation, Braunschweig, **1991**.

[6] V. Rozenberg, T. Danilova, E. Sergeeva, E. Vorontsov, Z. Starikova, K. Lysenko, Y. Belokon', *Eur. J. Org. Chem.* **2000**, 3295−3303.

[7] C. Reuter, G. Pawlitzki, U. Wörsdörfer, M. Plevoets, A. Mohry, T. Kubota, Y. Okamoto, F. Vögtle, *Eur. J. Org. Chem.* **2000**, 3059−3067.

[8] Th. Focken, H. Hopf, V. Snieckus, I. Dix, P. G. Jones, *Eur. J. Org. Chem.* **2001**, 2221−2228.

[9] A. Cipiciani, F. Fringuelli, V. Mancini, O. Piermatti, F. Pizzo, R. Ruzziconi, *J. Org. Chem.* **1997**, *62*, 3744 −3747.

[10] A. Cipiciani, F. Fringuelli, V. Mancini, O. Piermatti, A. M. Scappini, R. Ruzziconi, *Tetrahedron* **1997**, *53*, 11853−11858.

[11] D. Pamperin, B. Ohse, H. Hopf, M. Pietzsch, *J. Mol. Catal., B: Enzym.* **1998**, *5*, 317−319.

[12] J. Canceill, A. Collet, J. Gabard, G. Gottorelli, G. P. Spada, *J. Am. Chem. Soc.* **1985**, *107*, 1299−1308.

[13] [13a] W. Tochtermann, G. Olsson, C. Vögt, E.-M. Peters, K. Peters, H. G. von Schnering, *Chem. Ber.* **1987**, *120*, 1523−1532. [13b] J. Hilmer, Ph.D. dissertation, Technische Universität Braunschweig, **1991**.

[14] H. Gerlach, *Helv. Chim. Acta* **1978**, *61*, 2773−2776.

[15] F. R. Jensen, G. Goldman, in: *Friedel−Crafts and Related Reactions* (Ed.: G. A. Olah), Interscience, New York, **1964**, vol. III, part. 2, p. 1003.

[16] F. Bigi, G. Casiraghi, G. Casnati, G. Sartori, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2655−2657.

[17] A. Closse, W. Haeflinger, D. Hauser, H. U. Gubler, B. Dewold, M. Baggiolini, *J. Med. Chem.* **1981**, *24*, 1465−1471.

[18] M. Psiorz, R. Schmid, *Chem. Ber.* **1987**, *120*, 1825−1828.

[19] [19a] R. Stollé, E. Knebel, *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 1213−1220. [19b] D. J. Zwanenberg, W. A. Reynen, *Synthesis* **1976**, 624−625.

[20] [20a] R. Stollé, *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 1130−1132. [20b] D. Papa, E. Schwenk, H. F. Ginsberg, *J. Org. Chem.* **1949**, *14*, 723−731.

[21] P. G. Jones, W. Grahn, D. Remmers, P. Bubenitschek, *Z. Kristallogr.* **1994**, *209*, 459−460.

[22] H. Hopf, D. Barrett, *Liebigs Ann.* **1995**, 449−451.

[23] D. J. Cram, A. C. Day, *J. Org. Chem.* **1966**, *31*, 1227−1232.

[24] L. F. Fieser, M. Fieser, *Reagents for Organic Synthesis*, J. Wiley & Sons, New York, London, Sydney, **1968**, p. 815.

[25] K. Krohn, H. Rieger, H. Hopf, D. Barrett, P. G. Jones, D. Döring, *Chem. Ber.* **1990**, *123*, 1729−1732.

[26] G. M. Sheldrick, *SHELXTL PC Version 5.0, An integrated system for solving, refining, and displaying crystal structures from diffraction data*, Siemens Analytical X-ray Instruments Inc., Madison, WI, **1994**.

Received July 4, 2001
[O01328]