Chemoenzymatic Synthesis of Optically Pure Planar Chiral (*S*)-(–)-5-Formyl-4-hydroxy[2.2]paracyclophane

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The synthesis of optically pure (*S*)-5-formyl-4-hydroxy-[2.2]paracyclophane (*S*)-**3** (*ee* > 99 %) was achieved by a three-step chemoenzymatic procedure consisting of (i) kinetic enzymatic resolution of (*R,S*)-4-acetoxy[2.2]paracyclophane (*R,S*)-**1** to produce optically pure starting material, which after (ii) hydrolysis was subjected to (iii) stereoselective *ortho*-formylation with an overall yield of 51 %. All attempts to use a biocatalyst directly for the preparation of optically pure disubstituted [2.2]paracyclophanes failed because of either total lack of activity (bioreduction) or low enantioselectivities of the enzymes screened (hydrolases). Using the chemoenzymatic approach from (*R,S*)- **1**, optically pure (*S*)-**1** and after subjecting (*S*)-**1** to hydrolysis and finally to formylation (*S*)-**3** was obtained. As confirmed by chiral GC, hydrolysis and formylation took place without racemization. During the optimization of the enzymatical part of the synthesis a strong influence of both the nature of the cosolvent and the pH of the buffer-phase on the enantioselectivity value *E* were observed. Using a two-phase system consisting of diethyl ether and phosphate buffer an *E* value higher than 100 was achieved at a pH of 7.0 and at room temperature.

Introduction

The interest in the synthesis of optically pure planar-chiral ligands for transition-metal-catalyzed asymmetric synthesis is rapidly growing since such complexes are used as chiral catalysts for the preparation of enantiomerically pure compounds on an industrial scale. Recently, the multi-ton synthesis of the herbicide (*S*)-metolachlor by asymmetric hydrogenation was reported using a new class of planar-chiral (ferrocenyldiphosphane)iridium complexes[1].

Like ferrocene derivatives planar-chiral paracyclophanes are of growing interest, because of their chemical stability against oxidation and racemization under acidic or basic conditions[2]. Therefore, much effort was made to show that paracyclophanes are useful ligands in asymmetric synthesis, too. Recently, it has been shown by Vögtle et al. that dendrimers, bearing terminal planar chiral [2.2]paracyclophanes, can be employed for complexation of various metal cations and can therefore be foreseen as asymmetric homogenous catalysts[3]. On the other hand, disubstituted enantiomerically pure [2.2]paracyclophanes have been used as chiral auxiliaries in the transition-metal-catalyzed asymmetric synthesis of β-hydroxy-α-amino acids[3][4] and in asymmetric hydrogenation reactions[5].

Former attempts in the preparation of mono- and disubstituted [2.2]paracyclophanes included diastereomeric resolution[4][5][6][7] and separation by chiral HPLC[8], but the yields generally were too low to be useful in preparative terms.

In a previous paper we reported on the first preparatively useful biotransformation for the synthesis of an optically pure monosubstituted [2.2]paracyclophane[9]. (*S*)-4-formyl-[2.2]paracyclophane was synthesized by asymmetric reduction of the racemic substrate using whole cells of *Saccharomyces cerevisiae* as a biocatalyst. Recently, we[10] and others[11] similarily reported on the enzyme-catalyzed kinetic resolution of 4-acetoxy-[2.2]paracyclophane (**1**). Out of 28 enzymes screened, we found that lipase from *Candida rugosa* (formerly *Candida cylindracea*[12]), commercially available from Amano (Japan), showed the highest enantioselectivity. As can be seen from the literature[12] and our previous paper, lipase preparations from the same microorganism (*Candida rugosa*) obtained from different suppliers showed significant differences in enantioselectivity. This difference is possibly caused by the low purity of the commercial lipase preparations. In fact, up to four different lipases (two in each *Candida cylindracea* preparations tested) have been found in commercial lipase preparations as determined recently by activity staining experiments[13]. Because

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of the strong dependence of the enantioselectivity on the lipase preparation used, detailed information on the source of the enzyme is necessary which, unfortunately, is missing in the paper of Cipiciani et al.[11].

The present paper deals with our recent results on the preparative-scale synthesis of optically pure disubstituted [2.2]paracyclophanes which are of main interest as chiral auxiliaries in asymmetric synthesis as mentioned above. Investigations on the direct resolution of the disubstituted racemic substrate, as well as the development of a preparatively useful chemoenzymatic method for the synthesis of optically pure 5-formyl-4-hydroxy[2.2]paracyclophane **3** are discussed.

For the quantitative analysis of substrate and product enantiomers, a gas-chromatographic method was developed and optimizations were carried out on the basis of the reaction kinetics.

Results and Discussion

Investigations on the Kinetic Resolution of Racemic 5-Formyl-4-hydroxy[2.2]paracyclophane (3): Bioreduction and Hydrolysis

All microorganisms that have been previously shown to be able to reduce (monosubstituted) 4-formyl[2.2]paracyclophane to 4-hydroxymethyl[2.2]paracyclophane[9] were applied for the bioreduction of 5-formyl-4-hydroxy[2.2]paracyclophane (**3**). While (monosubstituted) 4-formyl[2.2]paracyclophane was reduced with good activity and high enantioselectivity, no reduction at all could be observed in the case of the disubstituted [2.2]paracyclophane.

For this reason, all hydrolases able to perform the kinetic resolution of (monosubstituted) 4-acetoxy[2.2]paracyclophane (**1**)[10] were tested for the resolution of 4-acetoxy-5-formyl[2.2]paracyclophane (**4**). However, no transesterification or esterification reactions were detectable. Hydrolysis gave only low enantiomeric ratios as shown in Table 1. During the reaction, the concentrations of the enantiomers of **3** and **4** were measured by chiral GC and the "*E* values" were calculated from the data obtained according to Chen et al.[14].

As can be seen from Table 1 and from the literature[10], under screening conditions the disubstituted [2.2]paracyclophane **4** is hydrolyzed by the same enzymes with significantly lower enantiomeric ratio than the monosubstituted [2.2]paracyclophane. The highest enantiomeric ratio was found for a *Mucor miehei* lipase preparation (Biocatalysts). Because all methods published so far for the synthesis of disubstituted **3** start from monosubstituted **1**, an enantioselective step can be introduced either at the beginning (enantioselective preparation of **1**) or at the end of the synthesis (enantioselective preparation of **3**). In both cases, a high enantioselectivity is required for a preparatively useful overall synthesis.

Table 1. Screening for hydrolases able to perform the stereoselective hydrolysis of 4-acetoxy-5-formyl-[2.2]paracyclophane (**4**) in the presence of toluene as a cosolvent; the *E* value was calculated using the model of Chen and Sih[14]

enzyme	source	supplier	*E* value
lipase	*Mucor miehei*	Biocatalysts	4.2
lipase	*Candida antarctica,* fraction A	Boehringer Mannheim	3.6
lipase	*Candida cylindracea*	Fluka	2.6
Alcaline Lipase	*Pseudomonas sp.*	Showa Denko	2.3
Lipase AY	*Candida rugosa*	Amano	2.0
lipase	*Rhizopus*	Solvay-Enzymes	1.7
lipase	*Candida rugosa*	Boehringer Mannheim	1.6
Lipase D	*Rhizopus delemar*	Amano	1.6
lipase	*Pseudomonas alcaligenes*	Gist-Brocades	1.5
Lipase A	*Aspergillus niger*	Amano	1.3
lipase	Porcine pancreas	Boehringer Mannheim	1.3
Lipase M	*Mucor javanicus*	Amano	1.2
lipase	*Pseudomonas fluorescens*	Biocatalysts	1.2
lipase	*Candida antarctica*	Amano	1.2
lipase	*Pseudomonas sp.*	Boehringer Mannheim	1.1
lipase	*Humicula sp.*	Boehringer Mannheim	1.1
lipase	*Humicola lanuginosa*	Biocatalysts	< 1.1
Lipase R	*Penicillium roquefortii*	Amano	< 1.1
Lipase F	*Rhizopus javanicus*	Amano	< 1.1
Lipase F	*Pseudomonas cepacia*	Amano	< 1.1
Lipase G	*Penicillium camembertii*	Amano	< 1.1
lipase	Porcine pancreas	Fluka	< 1.1
lipase	*Chromobacterium viscosum*	Asahi	< 1.1
lipase	*Burkholderia sp.*	Boehringer Mannheim	< 1.1
lipase	*Candida antarctica,* fraction B	Boehringer Mannheim	conversion < 10%[a]
lipase	*Mucor miehei*	Boehringer Mannheim	conversion < 10%[a]

No activity was found using the following enzymes: Lipase from *Mucor miehei* (Lipozym IM, Novo), lipase from *Candida antarctica* (Novozym 435, Novo).

[a] At this conversion, no *E* value could be calculated.

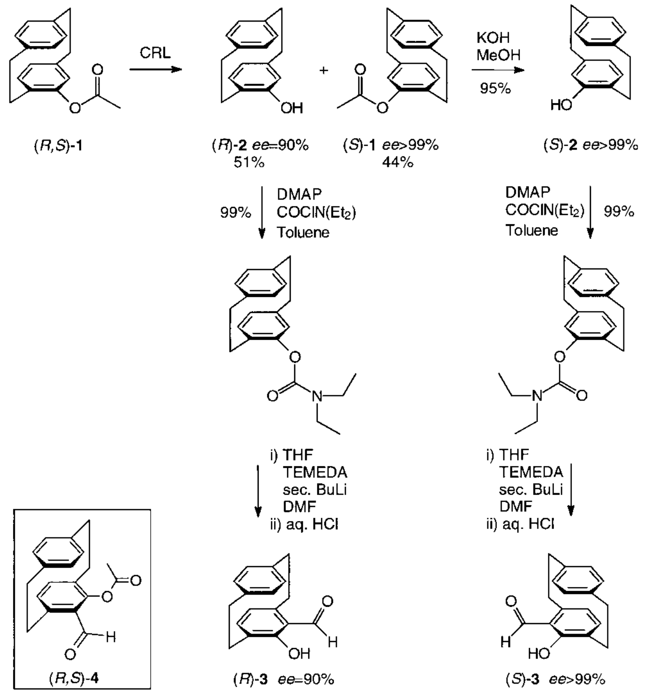
The enantioselectivity value $E = 20$, found under screening conditions for the preparation of (*S*)-**1**[10] using *Candida rugosa* lipase (CRL) from Amano (Japan), provides a more promising starting point for an optimization than the value $E = 4$, found for the kinetic resolution of **3**. We therefore decided to start with the first method, and to combine the enzymatic kinetic resolution of racemic **1** with the subsequent chemical *ortho*-formylation of the optically pure monosubstituted [2.2]paracyclophane (Scheme 1).

Optimization of the Reaction Conditions for the Enantioselective Hydrolysis of 4-Acetoxy[2.2]paracyclophane (1)

For hydrolase-catalyzed kinetic resolutions the chemical nature of a cosolvent, the pH of the buffer solution, the reaction temperature[15] and the proportion between cosolvent and buffer phase[16] had been previously shown to influence both the activity and the enantioselectivity of an enzyme.

The influence of the cosolvent on the enzymatic kinetic resolution of **1** was investigated first. Cosolvents were chosen according to their log *P* values[17] and used as described in the Experimental Section. As can be seen from Table 2, neither the activity nor the enantioselectivity value

Scheme 1. Chemoenzymatic synthesis of 5-formyl-4-hydroxy[2.2]paracyclophane (**3**)



seemed to be correlated with the log *P* value in case of the *Candida rugosa* lipase-catalyzed hydrolysis of **1**. With the exception of dodecane an increased enantioselectivity value relative to toluene (which was used for the initial screening) was determined for all cosolvents tested. Diethyl ether gave the best result (*E* > 100). As could be shown in additional experiments, the relation of the organic phase (diethyl ether) to the buffer phase did only influence the activity but not the enantioselectivity value (data not shown).

Table 2. Influence of organic cosolvents on the activity and the enantioselectivity of *Candida rugosa* lipase during the hydrolysis of 4-acetoxy[2.2]paracyclophane (**1**)

organic solvent	log *P*	activity[c] [U/mg protein × 10^{-5}]	*E* value
acetone[a]	−0.23	38.42	82
tetrahydrofuran[a]	0.49	0	no conversion
diethyl ether	0.85	4.46	> 100
hexanone	1.30	6.82	60
diisopropyl ether	1.88	8.83	30
chloroform	2.00	conversion < 10%[b]	conversion < 10%[b]
toluene	2.50	11.55	20
xylene	3.10	18.86	75
dodecane	6.59	14.81	4

[a] Gave a monophasic reaction mixture. – [b] At this conversion neither the activity nor the *E* value could be calculated. – [c] Activity was determined after 40 min.

Until now all attempts to link the observed enantioselectivity of enzymes to physicochemical data of the solvent were unsuccessful[15]. An interesting contribution to the present discussion was made recently by Wescott et al. who could quantitatively rationalize the energetics of desolvation of the enantiomers in the enzyme-bound transition states and could thereby explain experimental results of the solvent dependency of the enantioselectivity of a protease[18]. However, for this method the 3-D structure of an enzyme is required making the method only applicable to enzymes for which the structure is known.

Using diethyl ether as a cosolvent, the influence of the buffer pH was investigated. As can be seen from Table 3, the pH had an influence both on the enzymatic activity and on the enantioselectivity value of the reaction. In a relatively narrow range of pH = 5.5−8.0 the *E* value varied from 14 to > 100 with an optimum at pH = 7.0. In the literature the effect of the pH on the enantioselectivity of hydrolytic enzymes has been investigated only scarcely. For the porcine pancreas lipase (PPL) catalyzed hydrolysis of *meso*-2,3-epoxybutane-1,4-diol diacetate an optimum of pH = 6.5 was reported[19]. For the *Candida rugosa* lipase MY catalyzed hydrolysis of methyl *rac*-2-(4-hydroxyphenoxy)propionate the optimal activity had been found at pH = 6.0 (phosphate buffer) and the highest enantiomeric excess at pH = 4.0 (citrate buffer)[12]. The differences in pH optima for *Candida rugosa* lipase-catalyzed hydrolysis reactions may be explained by the inhomogeneity of the commercial sources as discussed above and should be investigated in more detail after further enzyme purification.

Table 3. Influence of the pH on activity and enantioselectivity of the *Candida rugosa* lipase-catalyzed hydrolysis of 4-acetoxy[2.2]paracyclophane (**1**)

pH	activity[a] [U/mg protein × 10^{-5}]	*E* value
5.5	1.74	39
6.0	1.97	62
6.5	2.04	73
7.0	5.68	> 100
7.5	2.40	31
8.0	0.86	14

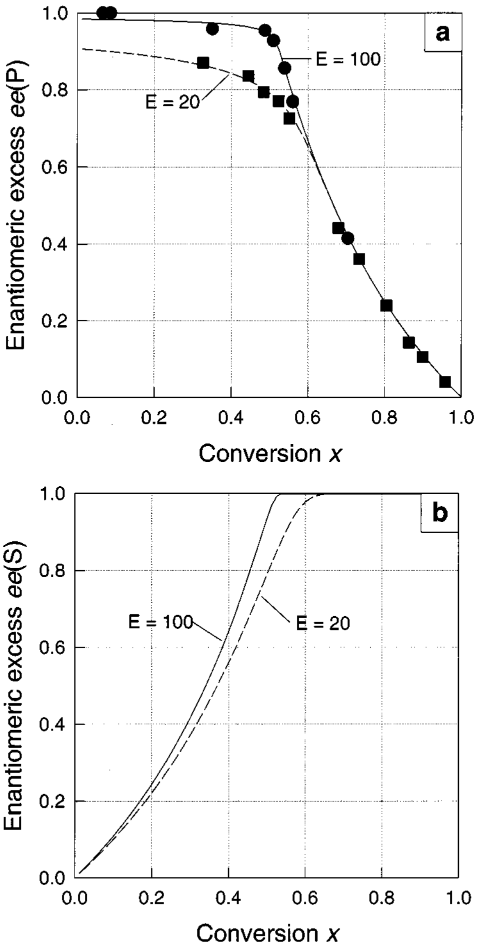
[a] Activity was determined after 120 min.

In Figure 1a and 1b typical reaction kinetics (*ee* versus conversion) are shown. For comparison, the results obtained before (dashed lines) and after (solid lines) optimization are shown. The concentrations of the product enantiomers [(*R*)-**2** and (*S*)-**2,** respectively] as well as the concentration of the substrate [(*R,S*)-**1**] were determined by gas chromatography. From the data obtained, the *E* value according to Chen et al.[14] was calculated (Figure 1a). Using the same model, the dependency of the enantiomeric excess of the substrate (**2**) on the conversion was calculated (Figure 1b) and was used as a basis for the design of the preparative-scale conversion. Using the mathematical model it was calculated that the enantiomeric excess of the substrate **1** is nearly 100% at a conversion of 53%.

Bioconversion of 4-Acetoxy[2.2]paracyclophane (1) on a Preparative Scale and Preparation of (*S*)-5-Formyl-4-hydroxy[2.2]paracyclophane [(*S*)-3]

Under optimized reaction conditions, 1.6 g of racemic **1** was subjected to the enzymatic kinetic resolution. The reaction was stopped at exactly 53% conversion and 0.7 g of

Figure 1. Enantiomeric excess of (a) the product {4-hydroxy[2.2]paracyclophane (**2**)} and the (b) the substrate {4-acetoxy[2.2]paracyclophane (**1**)} versus conversion before (■) and after (●) optimization; solid and dashed lines represent calculations using the model of Chen et al.[14]



optically pure (*S*)-**1** was isolated (*ee* > 99%). After hydrolysis, *ortho*-formylation of the optically pure (*S*)-**2** was carried out according to Hopf and Barrett using the *ortho*-metalation/formylation procedure developed by these authors for racemic **2**[20], and 285 mg of optically pure (*S*)-**3** (*ee* > 99%) was obtained from 430 mg of (*S*)-**2** (overall yield 51%). In an analogous way (*R*)-**2**, isolated after the kinetic resolution reaction (90% *ee*), was converted to optically active (*R*)-**3** (90% *ee*).

As discussed above, a possible alternative method employing the kinetic resolution of disubstituted [2.2]paracyclophane **3** would have required a shift of the enantioselectivity value from 4 to > 100. Because both methods start from racemic **1**, this alternative has no general advantages over the method developed and was therefore not further optimized.

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Experimental Section

General: Unless otherwise stated, all chemicals used were of reagent grade and purchased from Fluka (Deisenhofen, Germany). Racemic 4-hydroxy[2.2]paracyclophane (**2**)[21], and 5-formyl-4-hydroxy[2.2]paracyclophane (**3**)[20] were synthesized according to the literature. – For the synthesis of 4-acetoxy[2.2]paracyclophane (**1**) and 5-acetoxy-4-formyl[2.2]paracyclophane (**4**), the method described in the literature[20] for the synthesis of *O*-(4-[2.2]paracyclophanyl) diethylcarbamate was slightly modified. **1** was prepared from **2**, and **4** from **3**, using acetyl chloride instead of diethylcarbamoyl chloride and dichloromethane instead of toluene. The reaction mixture was refluxed for 36 h. – Lipases listed in Table 1 were either purchased or were gifts from Amano Pharmaceutical (Nagoya, Japan), Asahi Chemical Industry (Tokyo, Japan), Biocatalysts (Pontybridd, UK), Boehringer Mannheim (Penzberg, Germany), Showa Denko (Tokyo, Japan), Fluka (Neu-Ulm, Germany), Gist-Brocades (Delft, The Netherlands), Novo (Bagsvaerd, Denmark), and Solvay Enzymes (Hannover, Germany), respectively. – Optical rotations were determined using a polarimeter type 241 or 341 from Perkin-Elmer (Überlingen, Germany).

Screening for Stereoselective Reduction of 5-Formyl-4-hydroxy-[2.2]paracyclophane (**3**): Microorganisms and methods used in the screening for the bioreduction of **3** were essentially the same as described earlier for the reduction of 4-formyl[2.2]paracyclophane[9].

Screening for Stereoselective Hydrolysis of 4-Acetoxy-5-formyl-[2.2]paracyclophane (**4**): The screening for enzymes able to perform the stereoselective hydrolysis of **4** was carried out using a two-phase system due to the poor solubility of the substrate. The respective enzyme preparation (100 mg) was dissolved in 1.8 ml of 0.1 M potassium phosphate buffer at pH = 7.0, and the reaction was started by adding 1.2 ml of a solution of 3.8 mM of **4** in toluene. The reaction mixture was stirred at room temperature. After centrifugation, samples of the organic phase were taken and analyzed by thin-layer or gas chromatography.

Optimization of the Reaction Conditions for the Enantioselective Hydrolysis of 4-Acetoxy[2.2]paracyclophane (1)

Variation of Organic Cosolvents: Organic solvents listed in Table 2 were chosen according to the log *P* concept[17]. 50 mg of *Candida rugosa* lipase (Amano, Lot. No.: LAYS02519) were dissolved in 1.8 ml of 0.1 M potassium phosphate buffer (pH = 7.0). To start the reaction, 1.2 ml of a solution of **1** (5.9 mM) in the respective organic solvent was added. The reaction mixture was stirred at room temperature. Conversion of the reaction and enantiomeric excess of **2** formed during the reaction were determined by chiral gas chromatography.

Variation of pH: 30 mg of lipase from *Candida rugosa* (Amano, Lot. No.: LAYS02519) was dissolved in 1.8-ml aliquots of phosphate buffer (0.1 M) of pH = 5.5, 6.0, 6.5, 7.0, 7.5, and 8.0 and incubated at room temperature for 10 min. The reaction was started by addition of 1.2 ml of a 5.9 mM solution of **1** in diethyl ether. The reaction mixture was stirred at room temperature. Conversion of the reaction and enantiomeric excess of **2** formed during the reaction were determined by chiral gas chromatography.

Synthesis of (*S*)-*4-Acetoxy[2.2]paracyclophane* [(*S*)-**1**] *and (R)-4-Hydroxy[2.2]paracyclophane* [(*R*)-**2**] *on a Preparative Scale:* Optimized reaction conditions were used for the conversion of (*R,S*)-**1** on a preparative scale. 1.6 g of (*R,S*)-**1** (6.0 mmol) was dissolved in 76.8 ml of diethyl ether. To start the reaction, a solution of 3.0 g (17 kU) of *Candida rugosa* lipase (Amano, Lot. No.: LAYS02519) in 115.2 ml of 0.1 M phosphate buffer (pH = 7.0) was added to the substrate solution. The conversion was monitored by chiral gas chromatography. After 95 h, the reaction was stopped at 53% conversion by separation of the buffer phase and organic phase. The buffer phase was extracted twice with 100 ml of diethyl ether. The organic phases were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Compounds **1** and **2** were separated by low-pressure liquid chromatography (dichloromethane) and yielded 699 mg (2.62 mmol, 88%) of optically pure (*S*)-**1**; *ee* > 99%, mp 121°C (ref.[7] mp 122−123°C), $[\alpha]_D^{20} = +40.8$ {*c* = 0.93, $CHCl_3$, ref.[11] $[\alpha]_D^{20} = +41.2$ (*c* = 1.02)} and 682 mg (3.04 mmol, 51%) of optically active (*R*)-**2**; *ee* = 90%, mp 225°C (ref.[22] mp 223−228°C), $[\alpha]_D^{20} = +7.9$ {*c* = 1.13, $CHCl_3$, ref.[7] $[\alpha]_D^{20} = +8.4$ (*c* = 1.22)}. − MS and NMR spectra of both compounds were identical with those of racemic samples.

Synthesis of (S)-5-Formyl-4-hydroxy[2.2]paracyclophane [(*S*)-**3**]: A solution of 56.1 mg of potassium hydroxide in 40 ml of methanol (10 mmol) at 0°C was added slowly with stirring to a solution of 535.5 mg of (*S*)-**1** (2 mmol) in 100 ml of methanol. The reaction mixture was allowed to warm up to room temperature and was stirred overnight. Methanol was evaporated, and the residue was suspended in water (50 ml). The product was extracted with dichloromethane (3 × 50 ml). After drying with anhydrous $MgSO_4$, the solvent was evaporated to yield 430.6 mg (1.92 mmol, 95%) of (*S*)-**2**; *ee* > 99% (GC), mp 225°C, $[\alpha]_D^{20} = -8.2$ (*c* = 0.86, $CHCl_3$).

The synthesis of optically pure (*S*)-**3** was carried out according to the method published for the racemic [2.2]paracyclophane[20]. The crude product was purified by column chromatography (eluent CH_2Cl_2) instead of thick-layer chromatography.

Starting from 430 mg of (*S*)-**2** (1.92 mmol), 285 mg of (*S*)-**3** (1.3 mmol) was obtained (61%). Racemization of the optically pure product was not observed during the synthesis; *ee* > 99% (GC), mp 190°C (ref.[23] mp 201−204°C), $[\alpha]_D^{20} = -597$ {*c* = 0.1, $CHCl_3$, ref.[7] for (*R*)-**3** $[\alpha]_D^{20} = +587$ (*c* = 0.51, benzene)}. − MS and NMR spectra were identical with those of racemic samples.

Synthesis of (R)-5-Formyl-4-hydroxy-[2.2]paracyclophane [(*R*)-**3**]: 450 mg (2.0 mmol) of (*R*)-**2** obtained by kinetic resolution was converted to 160 mg (0.63 mmol, 31%) of (*R*)-**3** using the method described above for the preparation of (*S*)-**3**; *ee* > 90% (GC), mp 190°C (ref.[23] mp 201−204°C), $[\alpha]_D^{20} = +474$ {*c* = 0.1, $CHCl_3$, ref.[7] $[\alpha]_D^{20} = +587$ (*c* = 0.51, benzene)}. − MS and NMR spectra were identical with those of racemic samples.

Chromatography

Thin-Layer Chromatography: Thin-layer chromatography was performed using precoated silica plates (Polygram Sil G/UV_{254}, Macherey and Nagel, Düren, Germany; dichloromethane). R_f(**1**) = 0.59; R_f(**2**) = 0.31; R_f(**3**) = 0.74; R_f(**4**) = 0.50.

Chiral Gas Chromatography: The determination of the conversion of **1** and the enantiomeric excess of **2** were carried out as described before[10]. Separation of the enantiomers of **3** and **4** was carried out using the same equipment and a heptakis(2,3-di-*O*-methyl-6-*O*-dimethylthexylsilyl)-*β*-cyclodextrin (50% in polysiloxane OV 1701) column. At a pressure of 0.8 kPa, the following temperature program was applied: 145°C (50 min), 5°C/min to 160°C, 160°C (27 min). Under these conditions, separation factors α of the enantiomers were calculated to be 1.05 (**3**) and 1.02 (**4**), respectively. Retention times: (*R*)-**3**: 41.1 min; (*S*)-**3**: 43.2 min; (*S*)-**4**: 74.8 min; (*R*)-**4**: 76.1 min.

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