Regioselective Fries Rearrangement and Friedel−Crafts Acylation as Efficient Routes to Novel Enantiomerically Enriched *ortho*-Acylhydroxy[2.2]paracyclophanes

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Two useful approaches to *ortho*-acylhydroxy[2.2]paracyclophanes, starting from 4-hydroxy[2.2]paracyclophane, have been developed. $TiCl_4$-catalyzed Fries rearrangement and direct acylation occur regioselectively (to the *ortho* position with respect to the hydroxy group), leading to 4-acetyl-5-hydroxy[2.2]paracyclophane (**3**) and 4-benzoyl-5-hydroxy[2.2]paracyclophane (**4**) in high to excellent chemical yields. For compound **4**, an X-ray investigation has been performed. *ortho*-Acylhydroxy[2.2]paracyclophanes **3** and **4** have been obtained in enantiomerically enriched forms (*ee* 92–99%) and the absolute configurations of their enantiomers have been determined.

Introduction

During the last decade, [2.2]paracyclophane derivatives with planar chirality have become the subject of intensive investigations, because of their ability to act as a source of asymmetric induction in stereoselective processes. A number of successful applications have been reported of monosubstituted and differently (*ortho*-, *pseudo-ortho*-, *pseudo-gem*-)disubstituted chiral [2.2]paracyclophanyl derivatives acting as stoichiometric auxiliaries in asymmetric synthesis and as ligands in asymmetric catalysis.[1]

To date, only a few *ortho*-disubstituted compounds with two functional groups have been synthesized.[1c,1j,2,3] Among them, 4-formyl-5-hydroxy[2.2]paracyclophane (FHPC, a chiral analogue of salicylaldehyde) has been employed as an efficient chiral inductor in stoichiometric stereoselective synthesis of α-amino acids[1c,1d] and catalytic asymmetric trimethylsilylcyanation of benzaldehyde.[1g] [2.2]Paracyclophane-derived *N*-acyloxazol-2(3*H*)-one has been suggested as a suitable auxiliary for the enantioselective synthesis of β-hydroxy acids.[1j]

ortho-Acylhydroxy[2.2]paracyclophanes can be regarded as close relatives of FHPC, but they have not yet been synthesized. Bearing bulky substituents near the chiral [2.2]paracyclophanyl unit, these compounds could provide strong asymmetric induction in reactions in which they might function as potential chiral auxiliaries.

We report here the synthesis of *ortho*-acylhydroxy[2.2]paracyclophanes by highly regioselective Friedel−Crafts acylation of 4-hydroxy[2.2]paracyclophane (**1**) and Fries rearrangement of its *O*-acyl derivative **2**. In addition, two preparative routes to enantiomerically enriched *ortho*-acylhydroxy[2.2]paracyclophanes were elaborated.

Results and Discussion

ortho-Regioselective Fries Rearrangement

Fries rearrangement of phenolic esters in the presence of Lewis acids is one of the common routes to hydroxyaryl ketones.[4] Both *para* and *ortho* isomers are usually produced; their ratio is dependent on factors such as the catalyst used, temperature, solvent, substitution pattern, etc. Rearrangement of unsubstituted phenolic esters at room temperature leads to the formation of *para*-substituted phenols and is commonly kinetically favoured, whereas at high temperatures *para*-hydroxyaryl ketones rearrange to the corresponding *ortho* isomers. *ortho*-Substituted phenolic esters rearrange mostly at the *para* position, whereas *para*-substituted esters always rearrange to *ortho*-hydroxyaryl ketones. *meta*-Substitution favours *ortho* rearrangements because of the combination of electronic effects and steric hindrance at the *para* position.

For [2.2]paracyclophane phenolic esters, the Fries rearrangement has not to date been investigated. The only example of a related process (interpreted in the literature as an anionic Fries rearrangement) concerns *ortho*-lithiated *N*,*N*-diethylcarbamoyl[2.2]paracyclophane, which suffers a shift of the *N*,*N*-diethylcarbamoyl group to the corresponding *ortho*-substituted phenol.[2]

We studied a classic Fries rearrangement of 4-acetoxy-[2.2]paracyclophane (**2**) as a model reaction for carrying out the synthesis of *ortho*-acylhydroxy[2.2]paracyclophanes (Scheme 1). The ester **2**[5] was obtained in high yield by stirring a mixture of phenol **1**, acetyl chloride, and pyridine in dichloromethane at room temperature for 4 h.

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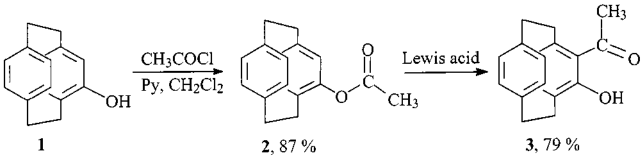


Scheme 1

Aluminium trichloride, used most frequently for Fries rearrangements of ordinary aromatic phenolic esters,[6] proved to be unsuitable in the rearrangement of [2.2]paracyclophane derivative **2**. Thus, refluxing of **2** in dichloroethane in the presence of 2 equiv. of $AlCl_3$ did not produce the target product even in traces. The starting material was consumed and a mixture of several unidentified compounds was formed (Table 1, Run 1). Very probably, migration of the ethano bridges of [2.2]paracyclophane had taken place under the influence of $HAlCl_4$[7] (similar migration or cleavages of alkyl fragments also occur during the rearrangement of ordinary alkyl-substituted phenolic esters in the presence of $AlCl_3$ under harsh conditions[8]). In the reactions of **2** with 1.3 equiv. of $AlCl_3$, a new compound was obtained and identified by ^1H NMR spectroscopy, mass spectrometry and elemental analysis as 4-acetyl-5-hydroxy[2.2]-paracyclophane (AHPC, **3**) (Scheme 1, Table 1, Runs 2−4). The yield of **3** was low even after 8 h of reflux in dichloroethane (Table 1, Run 3); starting material **2** was recovered in moderate yield, phenol **1** (10%) was isolated as a by-product, and no traces of the *para* isomer of **3** were detected. Longer reaction times (Table 1, Run 4) led to a decrease in the chemical yield of **3**, probably because of the destruction of the product, as well as the starting material, in the presence of $AlCl_3$.

The use of a less reactive Lewis acid such as $TiCl_4$ allowed undesired migration or cleavage of alkyl moieties during the Fries rearrangement of alkyl-substituted phenolic esters to be avoided.[9] When we used a twofold excess of $TiCl_4$ to rearrange **2** in nitrobenzene (60 °C, 6 h) the expected product was isolated from the reaction mixture after sequential decomposition of the corresponding Ti complexes with 6 N HCl and aq. NaOH, but the yield was disappointingly low (Table 1, Run 5). When the amount of the Lewis acid was decreased to 1.3 equiv., the rearrangement of **2** at room temperature took 48 h, with the complete conversion of **2** to give a 65% yield of **3** (Table 1, Run 6). It should be noted that, in this case, **3** was isolated after decomposition of the reaction mixture with 6 N HCl. With an increase in temperature to 100 °C, the yield of **3** dropped (Table 1, Run 7), due to formation of some unidentified oily decomposition products. At 60 °C the target ketone **3** was obtained in 75% yield and some quantities of starting material **2** were recovered (Table 1, Run 8). The best result in this series was achieved at 70 °C, when the starting material was consumed and **3** was isolated in 79% yield (Table 1, Run 9).

Thus, the Fries rearrangement of 4-acetoxy[2.2]paracyclophane (**2**), unlike the rearrangement of sterically hindered phenolic esters, always led under the described experimental conditions to the corresponding *ortho*-acylhydroxy[2.2]paracyclophane **3**. The regioselectivity of this reaction did not depend on the temperature and catalyst used; however, a good yield of the target product was achieved only with $TiCl_4$ at moderate temperatures.

ortho-Regioselective Friedel−Crafts Acylation

As an alternative route to hydroxyaryl ketones, the direct acylation of phenols has been widely investigated in aromatic series.[10−15] However, **1** has not to date been used as a substrate for this kind of transformation.

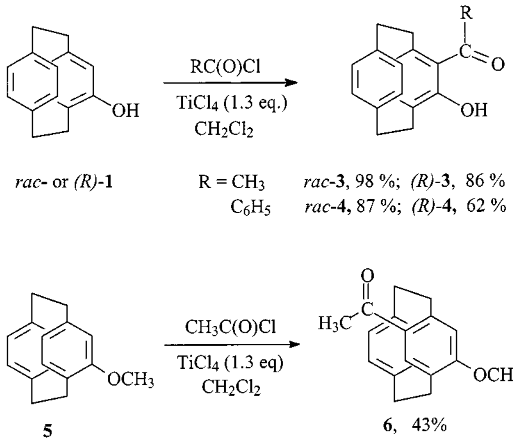
The stoichiometric acylation of phenols, promoted by strong Lewis acids (such as $AlCl_3$),[10] is generally unselective. To achieve good *ortho* regioselectivity in this reaction, an approach involving acylation (or alkylation) of Mg^{II}, Al^{III}, Ti^{IV},[11] Li,[12] or B^{III} [13] phenolates has been developed, the metal ions serving in this reaction as activating and *ortho*-directing agents.[14] Catalytic acylation of different phenol and 1-naphthol derivatives using Group 3 and 4 metal triflates also produced *ortho*-hydroxyaryl ketones in high chemical yields.[15]

$TiCl_4$ (1.3 equiv.) was selected to bring about Friedel−Crafts acylation of 4-hydroxy[2.2]paracyclophane, as the Fries rearrangement had been much more efficient with this catalyst than with $AlCl_3$. The acylation of **1** with acetyl chloride in CH_2Cl_2 was carried out (Scheme 2) at room temperature and the reaction was complete within 2 h, producing *ortho*-acylhydroxy[2.2]paracyclophane **3** in quantitative yield (> 98%). Acylation of **1** with benzoyl chloride under the same conditions was also *ortho*-regiose-

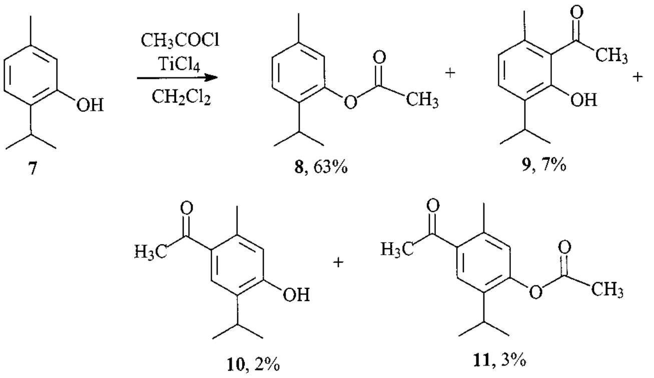
Table 1. Regioselective Fries rearrangement of 4-acetoxy[2.2]paracyclophane (**2**) to 4-acetyl-5-hydroxy[2.2]paracyclophane (**3**), promoted by Lewis acids

Run	Lewis acid	Solvent	*T* [°C]	Time [h]	Recovery of **2** (%)[a]	Yield of **3** (%)[a]
1	$AlCl_3$, 2 equiv.	$(CH_2Cl)_2$	83	6	−	−
2	$AlCl_3$, 1.3 equiv.	$(CH_2Cl)_2$	83	1	73	11
3	$AlCl_3$, 1.3 equiv.	$(CH_2Cl)_2$	83	8	35	34
4	$AlCl_3$, 1.3 equiv.	$(CH_2Cl)_2$	83	24	19	24
5	$TiCl_4$, 2 equiv.	$C_6H_5NO_2$	60	6	−	37
6	$TiCl_4$, 1.3 equiv.	$C_6H_5NO_2$	20	48	−	65
7	$TiCl_4$, 1.3 equiv.	$C_6H_5NO_2$	100	6	−	42
8	$TiCl_4$, 1.3 equiv.	$C_6H_5NO_2$	60	6	7	75
9	$TiCl_4$, 1.3 equiv.	$C_6H_5NO_2$	70	6	−	79

[a] Isolated yields.



Scheme 2



Scheme 3

lective and produced as the sole product a new 4-benzoyl-5-hydroxy[2.2]paracyclophane (BHPC, **4**) in 87% yield.

To account for the high regioselectivity of the acylation, we assumed that the reaction occurred by formation of an intermediate mixed complex of Ti^{IV} with substrate **1** and RCOCl, and that this complex played the key role in controlling the regioselectivity of the process. Indeed, when we carried out the acylation of 4-methoxy[2.2]paracyclophane (**5**) under the same conditions, the only product formed was the corresponding *para*-substituted ketone **6** (Scheme 2). It should also be noted that even after 21 h the reaction was not complete and the ratio of product **6**/starting material **5** was 83:17 as determined by ^1H NMR spectra of the reaction mixture. The yield of **6** after workup and preparative chromatography was 43%. In this case, the formation of the Ti^{IV} phenolate was impossible and acylation occurred at the less hindered *para* position of the aromatic ring.

We have carried out the acylation of sterically hindered 2-isopropyl-5-methylphenol (**7**) under the same conditions [$TiCl_4$ (1.3 equiv.), CH_2Cl_2, room temperature], to compare the relative reactivity of **1** with that of classic aromatic phenols (Scheme 3). The reaction produced a mixture of several compounds, which were separated by preparative chromatography and their structures elucidated on the basis of ^1H NMR and MS data. *O*-Acylated phenol derivative **8** was obtained as the main product (63%), together with three other *C*-acylated by-products **9−11**. Two *para*-substituted compounds, **10** and **11**, were formed in 2% and 3% yields, respectively, and the yield of *ortho*-hydroxyaryl ketone **9** was also low (7%).

Thus, we have found that, under the above conditions, direct acylation occurred with high *ortho* regioselectivity only in the case of 4-hydroxy[2.2]paracyclophane. This reaction was as highly *ortho*-regioselective as the Fries rearrangement; however, it could be carried out in a very simple manner, proceeded under milder conditions in a shorter time, and produced the target product with a noticeably increased yield. Thus, direct Friedel−Crafts acylation of **1** could be considered as a general and efficient route to *ortho*-acylhydroxy[2.2]paracyclophanes.

X-ray Crystallographic Study of 4-Benzoyl-5-hydroxy-[2.2]paracyclophane (4)

Single-crystal X-ray diffraction study of the ketone **4** has shown that the carbonyl oxygen atom of the ketone group and the hydrogen atom of the phenol group form an intramolecular hydrogen bond (Figure 1), as also observed in FHPC.[16]

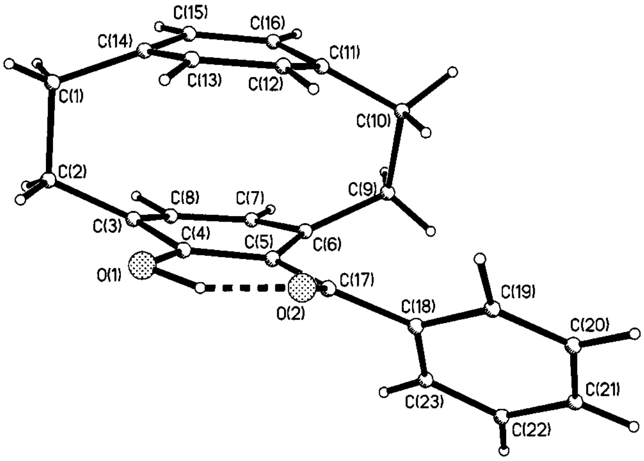


Figure 1. General view of 4-benzoyl-5-hydroxy[2.2]paracyclophane (**4**)

In two independent molecules, the phenyl rings form dihedral angles with the mean planes of the almost planar bicyclic systems HO(1)C(4)C(3)C(8)C(7)C(6)C(5)C(17)O(2) equal to 51.7(2)° and 50.6(2)°. The parameters of the hydrogen bonds O(1)−H···O(2) in the independent molecules are: H−O(1) = 1.07(6) and 1.08(8) Å, H···O(2) = 1.50(6) and 1.62(7) Å, O(1)···O(2) = 2.509(5) and 2.505(5) Å, O(1)HO(2) = 154(5) and 136(7)°.

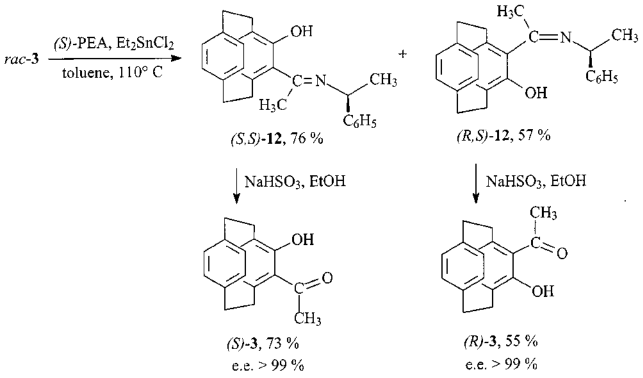
Additional information about the structure of the newly synthesized *ortho*-acylhydroxy[2.2]paracyclophanes was obtained from their spectroscopic data. The presence of the intermolecular hydrogen bond in solution was confirmed by the presence in the IR spectra of **3** and **4** ($c = 5\times10^{-3}$mol/L in CCl_4) of broad bands at 3200−2600 cm^{-1} and the relative shift of the C=O absorption band of **3** (1616 cm^{-1}) in comparison with 4-acetyl[2.2]paracyclophane (1680 cm^{-1}).[17]

In the ^{1}H NMR spectra of ketones **3** and **4** the signals of the OH group were detected as sharp singlets, which suggest the absence of a moderately rapid OH proton exchange (on the NMR timescale) and the existence of intramolecular hydrogen bonding between the OH and the carbonyl groups. In addition, in the spectrum of **4** we observe selective broadening of the *ortho*-H signal of the phenyl group, which is probably caused by slow rotation of this fragment around the C−C bond, resulting from its interaction with the protons of the sterically hindered [2.2]paracyclophanyl moiety.

Resolution of 3, Attempted Resolution of 4, and Determination of the Absolute Configurations of the Enantiomers of 3 and 4

For the resolution of *ortho*-acylhydroxy[2.2]paracyclophanes **3** and **4** into their enantiomers, we applied an approach previously successfully employed by us for the resolution of hydroxy aldehyde FHPC: namely the formation of diastereomeric Schiff bases, using (*S*)-α-phenylethylamine [(*S*)-α-PEA]. In general, the ketones react with primary amines more slowly than the aldehydes do, and so higher temperatures and longer reaction times are usually required. In addition, the removal of released water is necessary to shift this reversible reaction to completion. For the synthesis of sterically hindered ketimines bearing one or two aromatic groups, the application of drying agents such as molecular sieves[18] or $TiCl_4$[19] has been described.

All reactions of racemic **3** with (*S*)-α-PEA were carried out in refluxing toluene, with water removed by a Dean−Stark trap filled with $MgSO_4$. When $TiCl_4$ was employed, no traces of the corresponding Schiff bases were observed after 24 h. However, Et_2SnCl_2 was found to be an efficient catalyst for this reaction, and the relevant ketimine **12** was obtained in quantitative yield after 28 h, as an equimolar mixture of two diastereomers according to ^{1}H NMR data (Scheme 4).



Scheme 4

Diastereomeric ketimines **12** were separated by a combination of fractional crystallization and preparative chromatography, producing (*S*,*S*)-**12** ($[\alpha]_D^{25} = -232$, benzene) and (*R*,*S*)-**12** ($[\alpha]_D^{25} = +765$, benzene) (76 and 57% correspondingly) with diastereomeric purities greater than 99% as determined by ^{1}H NMR.

Both (*S*,*S*)-**12** and (*R*,*S*)-**12** seemed to be stable to acidic hydrolysis. Therefore, for the cleavage of the C=N bond, we used a method previously reported for sterically hindered oximes,[20] the hydrolysis of which included the formation of an intermediate bisulfite addition product. The individual diastereomers (*S*,*S*)-**12** and (*R*,*S*)-**12** were refluxed with sodium metabisulfite ($Na_2S_2O_5$) in 50% aqueous ethanol for 2.5 h, to produce enantiomerically enriched (*S*)-**3** ($[\alpha]_D^{25} = -550\pm10$, benzene) and (*R*)-**3** ($[\alpha]_D^{25} = +550\pm10$, benzene) in quantitative yield after workup (Scheme 4). As the enantiomeric purity of the resolving agent (*S*)-α-PEA was greater than 99%, the *ee* of (*S*)-**3** and (*R*)-**3** obtained in this way must also have been close to this value.

The absolute configurations of the enantiomers of **3** were determined by chemical transformation of (*R*)-**1** (*ee* 92%)[3] into (*R*)-**3** (Scheme 2), which was found to exhibit a positive rotation ($[\alpha]_D^{25} = +510$), and hence the configuration of the enantiomer of **3** with negative optical rotation was assigned as (*S*).

The reaction of racemic **4** with (*S*)-α-PEA was also carried out under conditions similar to those used with **3** (see Scheme 4). However, **4** did not form Schiff bases with (*S*)-α-PEA under the influence of Et_2SnCl_2. On the other hand, when an equimolar amount of $TiCl_4$ was used, the reaction was complete after 8 h, with the formation of the corresponding diastereomeric Schiff bases **13** in 91% chemical yield. Separation of diastereomeric ketimines **13** was carried out by fractional crystallization. Orange and bright red crystals were obtained in 73% and 36% overall chemical yields, respectively. X-ray analysis of both diastereomers revealed that the orange material had the (*S*,*S*) configuration (Figure 2), and the red material the (*R*,*S*) configuration (Figure 3). The diastereomeric purities of (*S*,*S*)-**13** ($[\alpha]_D^{25} = -468$, benzene) and (*R*,*S*)-**13** ($[\alpha]_D^{25} = +904$, benzene) were higher than 99%, by ^{1}H NMR.

Diastereometic ketimines **13** appeared to be extremely stable to hydrolysis by aqueous HCl and CF_3COOH, and also to hydrolysis via preliminary formation of an intermediate derivative with sodium metabisulfite or nitrosonium tetrafluoroborate. This prompted us to synthesize enantiomerically enriched (*R*)-**4** ($[\alpha]_D^{25} = +250$) from the corresponding (*R*)-**1** (92% *ee*) in accordance with Scheme 2. As expected, this compound reacted with (*S*)-α-PEA in the presence of $TiCl_4$ with the formation of the corresponding (*R*,*S*)-**13** ($[\alpha]_D^{25} = +864$, benzene).

X-ray Crystallographic Study of the Diastereomeric Schiff Bases 13

The X-ray investigations of diastereomeric ketimines (*R*,*S*)-**13** and (*S*,*S*)-**13** (see Figure 2 and 3) revealed that extremely short intramolecular N−H···O (in (*R*,*S*)-**13**) and N···H−O (in (*S*,*S*)-**13**) bonds are formed in the keto imine fragment of both molecules (hydrogen bond parameters in (*R*,*S*)-**13**: N(1)−H1(N)···O(1): N···O 2.497(2) Å, H···O 1.69(3) Å, NHO 140(2)°; in two independent molecules in the crystal structure of (*S*,*S*)-**13**: O(1)−H1(O)···N(1): O···N

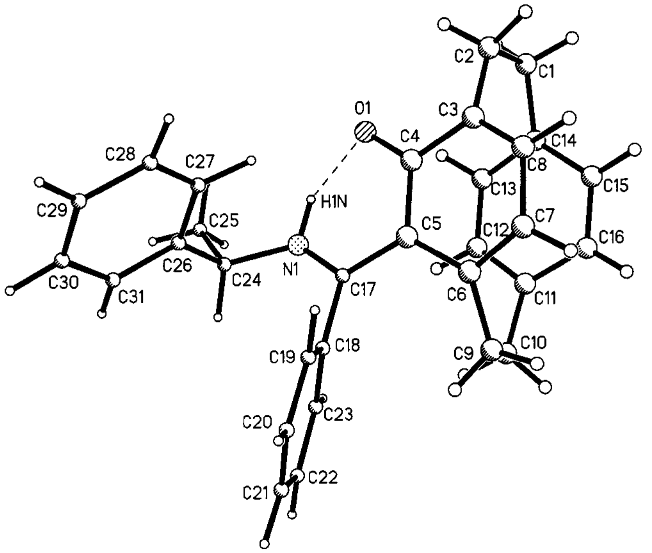


Figure 2. General view of (R,S)-**13**; selected bond lengths [Å] in the H-bonded ring: O(1)−C(4) 1.289(2), N(1)−C(17) 1.318(3), C(17)−C(5) 1.436(3), C(4)−C(5) 1.454(3)

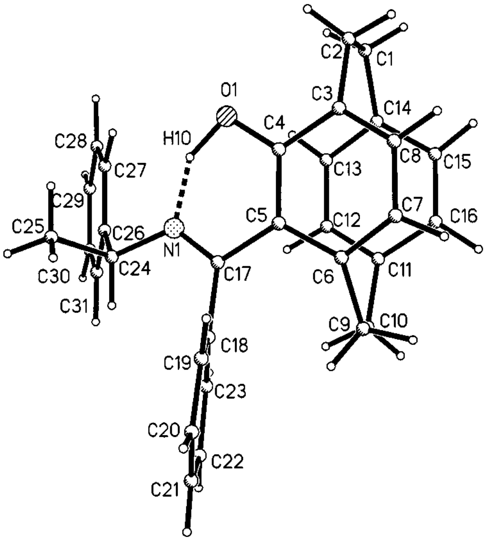


Figure 3. General view of (S,S)-**13**; selected bond lengths [Å] in the H-bonded ring, for two independent molecules: O(1)−C(4) 1.348(2) and 1.358(2), N(1)−C(17) 1.300(2) and 1.302(2), C(5)−C(17) 1.488(2) and 1.475(3), C(4)−C(5) 1.416(3) and 1.413(3)

2.465(2) and 2.487(2) Å, H···N 1.45(3) and 1.50(3) Å, OHN 150(2) and 153(2)°.

Conclusion

This study has demonstrated that the efficient introduction of an acyl group into the *ortho* position of 4-hydroxy[2.2]paracyclophane can be carried out either by Fries rearrangement of the corresponding intermediate *O*-acyl derivative, or by direct acylation of the phenol **1** with different acyl chlorides. $TiCl_4$ was found to be a catalyst of choice for both reactions. Two general approaches to enantiomerically enriched *ortho*-acylhydroxy[2.2]paracyclophanes were suggested: by the resolution of the racemic compounds via their diastereomeric Schiff bases with (*S*)-α-phenylethylamine, or by Friedel−Crafts acylation of enantiomerically enriched phenol **1**.

Experimental Section

General: Dichloromethane and (*S*)-α-phenylethylamine were purchased from Merck and used without purification. Nitrobenzene was purchased from Fluka and used without purification. Dichloroethane was washed successively with conc. H_2SO_4, water and saturated aq. Na_2CO_3, dried with $CaCl_2$, distilled twice from P_2O_5 and CaH_2, and stored over CaH_2 under argon. Acetyl chloride and benzoyl chloride were distilled twice from K_2CO_3. (*R*)-4-Hydroxy[2.2]paracyclophane was obtained in accordance with described procedures.[3] TLC analyses were performed on Silufol UV-254 precoated silica gel plates (Chemapol). Column chromatography was performed on Kieselgel 60 (Merck). − NMR: Bruker AMX-400 (400.13 MHz for ^1H), $CDCl_3$ as solvent, δ_H ($CHCl_3$ impurity) = 7.27. In the description of ^1H NMR spectra aromatic protons of the [2.2]paracyclophane (PC) moiety are marked as "PC aromatic *H*". − MS: KRATOS MS890A (70 eV). − IR: SPECORD M 82. − Optical rotations were measured with a Perkin−Elmer-241 polarimeter in a cell maintained by thermostat at 20 or 25 °C.

***O*-Acylation of 4-Hydroxy[2.2]paracyclophane with Acetyl Chloride:** To a solution of **1** (5 g, 0.022 mol) in CH_2Cl_2 (100 mL) pyridine (3.6 mL, 3.5 g, 0.045 mol) and acetyl chloride (3.2 mL, 3.5 g, 0.045 mol) were added. The orange mixture was stirred at room temperature for 4 h. The mixture was acidified to pH = 2 with 2 N HCl, then neutralized with Na_2CO_3, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with H_2O (3 × 15 mL) and dried with Na_2SO_4. The solvent was evaporated in vacuo and the crude product was purified by column chromatography on SiO_2 (CH_2Cl_2 as eluent) to yield 5.28 g (89%) of 4-acetoxy[2.2]paracyclophane (**2**) as a white powder. Analytically pure **2** (5.19 g, 87%) was obtained by recrystallization from heptane. M.p. 133−134 °C. (ref.[5] m.p. 132.5−133.5 °C).

Fries Rearrangement of 4-Acetoxy[2.2]paracyclophane (2) with $AlCl_3$: A suspension of **2** (0.15 g, 0.00056 mol) and $AlCl_3$ (0.098 g, 0.00073 mol) in 1,2-dichloroethane (6 mL) was refluxed for 8 h under an inert gas. The reaction mixture was cooled to room temperature, diluted with 15 mL of CH_2Cl_2 and hydrolyzed with 7 mL of 6 N HCl. The organic fraction was washed with H_2O (3 × 10 mL) and dried with Na_2SO_4. The solvent was evaporated in vacuo and the residue was separated by column chromatography on SiO_2 [CH_2Cl_2 or $CHCl_3$/Et_2O (20:1) as eluent] to yield 0.05 g (34%) of 4-acetyl-5-hydroxy[2.2]paracyclophane (**3**), 0.052 g (35%) of starting material **2** and 0.015 g (10%) of **1**. An analytically pure sample of **3** (0.03 g, 20%) was obtained as yellow crystals by recrystallization from heptane. − M.p. 115−116 °C. − ^1H NMR ($CDCl_3$): δ = 2.58 (s, 3 H, CH_3), 2.52−2.65 (m, 1 H, $-CHH-CH_2-$), 2.70−2.85 (m, 1 H, $-CHH-CH_2-$), 2.95−3.08 (m, 2 H, $-CHH-CH_2-$), 3.10−3.27 (m, 2 H, $-CHH-CH_2-$), 3.40−3.58 (m, 1 H, $-CHH-CH_2-$), 3.60−3.75 (m, 1 H, $-CHH-CH_2-$), 6.31 (d, ^3J = 7.8 Hz, 1 H, PC aromatic H^7 or H^8), 6.32 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{12} or H^{13}), 6.45 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{15} or H^{16}), 6.55 (d, ^3J = 7.8 Hz, 1 H, PC aromatic H^7 or H^8), 6.63 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{15} or H^{16}), 6.98 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{12} or H^{13}), 12.80 (s, 1 H, O*H*). − IR (CCl_4, c = 5 ×

10^{-3}mol/L): $\tilde{\nu}$ = 3200−2600 cm^{-1} (OH), 1616 (C=O). − $C_{18}H_{18}O_2$ (266.32): calcd. C 81.17, H 6.81; found C 81.42, H 6.93.

Fries Rearrangement of 4-Acetoxy[2.2]paracyclophane (2) with $TiCl_4$: To a solution of **2** (3.06 g, 0.012 mol) in nitrobenzene (18 mL) $TiCl_4$ (1.65 mL, 2.85 g, 0.015 mol) was added at 0 °C. The resulting dark cherry-colored solution was stirred for 6 h at 70 °C. The reaction mixture was diluted with 15 mL of CH_2Cl_2 and hydrolyzed with 7 mL of 6 N HCl. Organic fractions were washed with H_2O (3 × 10 mL) and dried with Na_2SO_4. The solvent was evaporated in vacuo and the crude product was purified by column chromatography on SiO_2 [CH_2Cl_2 or $CHCl_3/Et_2O$ (20:1) as eluent] to yield 2.5 g (79%) of 4-acetyl-5-hydroxy[2.2]paracyclophane (**3**) as yellow crystals. M.p. and ^1H NMR data are identical to those of **3** prepared by Fries rearrangement with $AlCl_3$.

Acylation of 4-Hydroxy[2.2]paracyclophane (1) with Acetyl Chloride: To a solution of **1** (0.84 g, 0.0038 mol) in CH_2Cl_2 (30 mL) $TiCl_4$ (0.54 mL, 0.94 g, 0.0049 mol) and acetyl chloride (0.27 mL, 0.3 g, 0.0038 mol) were successively added at 0 °C. The resulting dark cherry-colored solution was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C, diluted with 50 mL of H_2O and stirred for 15 min. The yellow organic layer was washed with H_2O (2 × 60 mL) and dried with Na_2SO_4. The crude product was obtained after removal of the solvent in vacuo and purified by column chromatography (SiO_2, eluent CH_2Cl_2) to yield 0.99 g (98%) of **3**. M.p. and ^1H NMR data are identical to those of **3** prepared by Fries rearrangement.

Acylation of 4-Hydroxy[2.2]paracyclophane (1) with Benzoyl Chloride: To a solution of **1** (0.5 g, 0.0022 mol) in CH_2Cl_2 (25 mL) $TiCl_4$ (0.32 mL, 0.55 g, 0.003 mol) and benzoyl chloride (0.26 mL, 0.31 g, 0.0023 mol) were successively added at 0 °C. The resulting dark cherry colored solution was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C, diluted with 50 mL of H_2O and stirred for 15 min. The yellow organic layer was washed with H_2O (2 × 60 mL), dried with Na_2SO_4 and the solvent was evaporated in vacuo to yield, after recrystallization from heptane, 0.62 g (87%) of 4-benzoyl-5-hydroxy[2.2]paracyclophane (**4**) as yellow crystals (pure by ^1H NMR). An analytically pure sample of **4** (0.33 g, 46%) was prepared by further recrystallization from heptane. − M.p. 181.5−183 °C. − ^1H NMR ($CDCl_3$): δ = 2.40−2.69 (m, 4 H, −C*H*H−CH_2−), 2.82−2.90 (m, 1 H, −C*H*H−CH_2−), 3.03−3.14 (m, 1 H, −C*H*H−CH_2−), 3.18−3.28 (m, 1 H, −C*H*H−CH_2−), 3.45−3.55 (m, 1 H, −C*H*H−CH_2−), 6.34 (d,^3J = 7.8, 1 H, PC aromatic H^7 or H^8), 6.47 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{12} or H^{13}), 6.50 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{15} or H^{16}), 6.58 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{15} or H^{16}), 6.63 (d, ^3J = 7.8 Hz, 1 H, PC aromatic H^7 or H^8), 7.09 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{12} or H^{13}), 7.46 (br. t, 2 H, aromatic *m-H*), 7.58 (br. t, 1 H, aromatic *p-H*), 7.73 (br. d, 2 H, aromatic *o-H*), 11.94 (s, 1 H, O*H*). − IR (CCl_4, *c* = 5 × 10^{-3}mol/L): $\tilde{\nu}$ = 3200−2600 cm^{-1} (OH); IR (nujol): $\tilde{\nu}$ = 1594 (C=O). − $C_{23}H_{20}O_2$ (328.41) calcd. 84.12, H 6.14; found C 84.25, H 6.27.

X-ray Crystallographic Study of 4-Benzoyl-5-hydroxy[2.2]paracyclophane (4): Crystal data: $C_{23}H_{20}O_2$, MW = 328.41, yellow plates, dimensions 0.7 × 0.4 × 0.3 mm, $d_{calcd.}$ = 1.293 g cm^{-1}, orthorhombic, space group $Pca2_1$ (no. 29), a = 7.821(3) Å, b = 18.846(5) Å, c = 22.883(7) Å, V = 3373(2) $Å^3$, Z = 8, F(000) = 1392. A total of 3507 reflections were recorded with an Enraf-Nonius CAD4 diffractometer [T = 293 K, graphite monochromator, $\lambda(\text{Mo-}K_\alpha)$ = 0.71073 Å, Θ-5/3Θ scan technique, no absorption correlation was applied, $\mu(\text{Mo-}K_\alpha)$ = 0.081 mm^{-1}, Θ = 2−26°]. Of these, 3399 independent reflections were used for the structure solutions (SHELXTL Plus 5[21]). The structure was solved by direct method, the non-hydrogen atoms were refined by full-matrix least-squares technique on F^2 in anisotropic approximation. All hydrogen atoms were located in the difference Fourier syntheses and included in the refinement in the isotropic approximation. Final discrepancy factors: $R1$ = 0.0374 [on F for 2025 reflections with $I > 2\,\sigma(I)$], $wR2$ = 0.1484 (on F^2 for all 3348 reflections used in the refinement 611 parameters). Largest difference peak and hole 0.140 and −0.127 $eÅ^{-3}$. Atomic coordinates, full bond lengths and angles, and thermal parameters are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (deposition number CCDC-137928).

Acylation of 4-Methoxy[2.2]paracyclophane (5) with Acetyl Chloride: To a suspension of **5** (0.04 g, 0.00017 mol) in CH_2Cl_2 (4 mL) $TiCl_4$ (0.024 mL, 0.04 g, 0.00022 mol) and acetyl chloride (0.012 mL, 0.013 g, 0.00017 mmol) were added successively at 0 °C. The resulting dark cherry-colored solution was stirred at room temperature for 21 h. The reaction mixture was cooled to 0 °C, diluted with 7 mL of H_2O and stirred for 15 min. The organic layer was 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 (SiO_2, eluent C_6H_6), yield 0.020 g (43%) of 4-acetyl-7-methoxy[2.2]paracyclophane (**6**) as a white powder. M.p. 143−145 °C. − ^1H NMR ($CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 2.53−2.63 (m, 1 H, −C*H*H−CH_2−), 2.68−2.76 (m, 1 H, −C*H*H−CH_2−), 3.00−3.20 (m, 4 H, −C*H*H−CH_2−), 3.33−3.48 (m, 1 H, −C*H*H−CH_2−), 3.78 (s, 3 H, OCH_3), 4.05−4.18 (m, 1 H, −C*H*H−CH_2−), 5.7 (s, 1 H, PC aromatic H^5), 6.35 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic *H*), 6.48 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic *H*), 6.51 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic *H*) 6.72 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic *H*), 6.93 (s, 1 H, H^8). − IR (nujol): $\tilde{\nu}$ = 1670 cm^{-1} (C=O). − IR (KBr): $\tilde{\nu}$ = 2854 cm^{-1} (OCH_3). − MS (70 eV); *m*/*z* (%): 280 (90) [M^+], 176 (100), 161 (33), 147 (86), 131 (30), 104 (87).

Acylation of 2-Isopropyl-5-methylphenol (7) with Acetyl Chloride: To a solution of **7** (0.40 g, 0.0027 mol) in CH_2Cl_2 (10 mL) $TiCl_4$ (0.38 mL, 0.0035 mol) and acetyl chloride (0.19 mL, 0.21 g, 0.0027 mol) were successively added at 0 °C. The resulting dark cherry-colored solution was stirred at room temperature for 40 h. The reaction mixture was cooled to 0 °C, diluted with 20 mL of H_2O and stirred for 15 min. The organic layer was washed with H_2O (2 × 30 mL) and dried with Na_2SO_4. Compounds **8−11** were separated by column chromatography (SiO_2, C_6H_6), and 0.062 g (15.5%) of starting material **7** was also recovered.

2-Isopropyl-5-methylphenyl Acetate (8): 0.321 g (63%), colorless oil. − ^1H NMR ($CDCl_3$): δ = 1.22 [d, ^3J = 6.9 Hz, 6 H, CH(CH_3)$_2$], 2.34 [s, 6 H, CH_3-Ar and C(O)−CH_3], 3.01 [sept, ^3J = 6.9 Hz, 1 H, C*H*(CH_3)$_2$], 6.85 (s, 1 H, aromatic H^6), 7.02 (br. d, ^3J = 7.8 Hz, 1 H, aromatic H^4), 7.19 (d, ^3J = 7.8 Hz, 1 H, aromatic H^3). − MS (70 eV); *m*/*z* (%): 192 (2) [M^+], 150 (14), 135 (49), 44 (28).

2-Hydroxy-3-isopropyl-6-methylphenyl Methyl Ketone (9): 0.035 g (7%), yellow oil. − ^1H NMR ($CDCl_3$): δ = 1.23 [d, ^3J = 6.9 Hz, 6 H, CH(CH_3)$_2$], 2.58 [s, 3 H, CH_3-Ar or C(O)−CH_3], 2.67 [s, 3 H, CH_3-Ar or C(O)−CH_3], 3.36 [sept, ^3J = 6.9 Hz, 1 H, C*H*(CH_3)$_2$], 6.70 (d, ^3J = 7.8 Hz, 1 H, aromatic *H*), 7.25 (d, ^3J = 7.8 Hz, 1 H, aromatic *H*), 12.67 (1 H, O*H*). − MS (70 eV); *m*/*z* (%): 192 (5) [M^+], 177 (16), 149 (25), 43 (85).

4-Hydroxy-5-isopropyl-2-methylphenyl Methyl Ketone (10): 0.010 g (2%), colorless crystals: − M.p. 126 °C. − ^1H NMR ($CDCl_3$): δ =

1.29 [d, ^3J = 6.9 Hz, 6 H, CH(CH_3)$_2$], 2.50 [s, 3 H, CH_3-Ar or C(O)−CH_3], 2.58 [s, 3 H, CH_3-Ar or C(O)−CH_3], 3.24 [sept, ^3J = 6.9 Hz, 1 H, CH(CH$_3$)$_2$], 6.1 (br. s, 1 H, O*H*), 6.65 (s, 1 H, aromatic H^6), 7.65 (s, 1 H, aromatic H^3). − MS (70 eV); *m*/*z* (%): 192 (73) [M$^+$], 177 (95), 161 (16), 134 (24), 91 (52), 77 (52), 43 (100).

4-Acetyl-2-isopropyl-5-methylphenyl Acetate (11): 0.020 g (3%), colorless oil: − ^{1}H NMR (CDCl$_3$): δ = 1.25 [d, ^3J = 7.15 Hz, 6 H, CH(CH_3)$_2$], 2.33 (s, 3 H, CH_3), 2.50 (s, 3 H, CH_3), 2.57 (s, 3 H, CH_3), 3.05 [sept, ^3J = 6.9 Hz, 1 H, CH(CH$_3$)$_2$], 6.77 (s, 1 H, aromatic H^6), 7.64 (s, 1 H, aromatic H^3). − MS (70 eV); *m*/*z* (%): 234 (1) [M$^+$], 192 (11), 177 (40), 149 (70), 43 (86).

Resolution of 4-Acetyl-5-hydroxy[2.2]paracyclophane into Its Enantiomers: To a solution of racemic **2** (0.85 g, 0.0032 mol) in toluene (30 mL) (*S*)-α-PEA (0.41 mL, 0.39 g, 0.00032 mol) and Et$_2$SnCl$_2$ (catalytic quantity) were added, and the mixture was refluxed for 28 h in a flask equipped with a Dean−Stark trap filled with MgSO$_4$. The solvent was removed in vacuo to produce in quantitative yield the mixture of diastereomeric 4-hydroxy-5-[1-(1-phenylethylimino)ethyl][2.2]paracyclophane [(*R*,*S*)- and (*S*,*S*)-**12**], in equimolar ratio (according to ^{1}H NMR). The mixture was recrystallized from 30 mL of hexane and the resulting orange precipitate (0.42 g) was then recrystallized from 9 mL of hexane, producing 0.283 g (48%) of diastereomerically pure (*S*,*S*)-**12**. The filtrates were combined and concentrated, and the residue was crystallized from 7 mL of hexane; further crops of enriched (*S*,*S*)-**12** (0.182 g) were obtained, then after some time 0.15 g of enriched (*R*,*S*)-**12** precipitated from the same solution. The filtrates were combined and concentrated, and the residue (0.64 g) was chromatographed on SiO$_2$ (C$_6$H$_6$/EtOH, 40:1). (*R*,*S*)-**12** (0.41 g) was obtained from the fractions with R_f = 0.46 and (*S*,*S*)-**12** (0.1 g) was obtained from the fractions with R_f = 0.27. The material with R_f = 0.46 was combined with the enriched (*R*,*S*)-**12**, and the material was recrystallized from 30 mL of hexane to give 0.34 g (57%) of diastereomerically pure (*R*,*S*)-**12**. The material with R_f = 0.27 was combined with the enriched (*S*,*S*)-**12**, and recrystallization from 10 mL of hexane produced an additional 0.168 g (28%) of diastereomerically pure (*S*,*S*)-**12**. The diastereomeric purity of (*S*,*S*)-**12** and (*R*,*S*)-**12** was monitored by TLC (benzene/ethanol, 40:1) and quantitatively determined by ^{1}H NMR.

Diastereomer (*S*,*S*)-12: Total yield 0.45 g (76%). − M.p. 165−166 °C. − $[\alpha]_D^{25}$= −232 (*c* = 0.4, C$_6$H$_6$). − ^{1}H NMR (CDCl$_3$), δ = 1.7 (d, ^3J = 6.54 Hz, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 2.33−2.43 (m, 1 H, −C*H*H−CH$_2$−), 2.50−2.58 (m, 1 H, −C*H*H−CH$_2$−), 2.79−2.89 (m, 1 H, −C*H*H−CH$_2$−), 2.93−3.06 (m, 2 H, −C*H*H−CH$_2$−), 3.14−3.39 (m, 2 H, −C*H*H−CH$_2$−), 3.38−3.48 (m, 1 H, −C*H*H−CH$_2$−), 4.87 (q, ^3J = 6.5 Hz, 1 H, α-*H*), 6.10 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{12} or H^{13}), 6.18 (d, ^3J = 7.8 Hz, 1 H, PC aromatic H^7 or H^8), 6.42 (d, ^3J = 7.8 Hz, 1 H, PC aromatic H^7 or H^8), 6.47 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{15} or H^{16}), 6.57 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{15} or H^{16}), 7.01 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{12} or H^{13}), 7.33 (br. t, aromatic *p*-*H*, 1 H), 7.45 (br. t, aromatic *m*-*H*, 2 H), 7.53 (br. d, aromatic *o*-*H*, 2 H), 15.74 (s, 1 H, O*H*). − C$_{26}$H$_{27}$NO (369.51) calcd. C 84.51, H 7.37, N 3.79; found C 84.55, H 7.54, N 3.76.

Diastereomer (*R*,*S*)-12: Total yield 0.34 g (57%). − M.p. 131.5−132.5 °C. − $[\alpha]_D$= + 765 (*c* = 0.4, C$_6$H$_6$). − ^{1}H NMR (CDCl$_3$), δ = 1.76 (d, ^3J = 6.5 Hz, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 2.47−2.70 (m, 2 H, −C*H*H−CH$_2$−), 2.83−3.25 (m, 4 H, −C*H*H−CH$_2$−), 3.34−3.49 (m, 2 H, −C*H*H−CH$_2$−), 4.90 (q, ^3J = 6.5 Hz, 1 H, α-*H*), 6.20 (d, ^3J = 7.8 Hz, 1 H, PC aromatic H^7 or H^8), 6.40−6.46 (m, 2 H, PC aromatic *H*), 6.50 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{15} or H^{16}), 6.63 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic H^{15} or H^{16}), 7.05 (dd, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic *H*), 7.30−7.38 (m, 5 H, aromatic *H*), 15.78 (s, 1 H, O*H*). − C$_{26}$H$_{27}$NO (369.51) calcd. 84.51, H 7.37, N 3.79; found C 84.23, H 7.21, N 3.56.

Hydrolysis of (*R*,*S*)-12: To a solution of (*R*,*S*)-**12** (0.227 g, 0.0006 mol) in 96% EtOH (10 mL) H$_2$O (4.6 mL) and Na$_2$S$_2$O$_5$ (0.41 g, 0.0022 mol) were added, and the mixture was refluxed for 2.5 h. The mixture was cooled to room temperature and an excess of 2 N HCl was added to adjust to pH = 7. The mixture was extracted with benzene (3 × 20 mL), and the bright yellow organic solution was successively washed with H$_2$O (2 × 20 mL), saturated aq. Na$_2$CO$_3$ (20 mL), and H$_2$O (20 mL), and dried with MgSO$_4$. After evaporation of the solvent in vacuo and purification of the solid residue on SiO$_2$ (eluent C$_6$H$_6$), 0.157 g (96%) of (*R*)-**3** was isolated. An analytically pure sample of (*R*)-**3** was obtained by recrystallization from hexane. − M.p. 71.5−72.5°C. − $[\alpha]_D^{25}$ = + 550±10 (*c* = 0.4, C$_6$H$_6$). − C$_{18}$H$_{18}$O$_2$ (266.32): calcd. C 81.17, H 6.81; found C 81.15, H 6.86. − ^{1}H NMR data are identical to those of racemic sample.

Hydrolysis of (*S*,*S*)-12: The procedure described above was applied to (*S*,*S*)-**12** (0.3 g, 0.0008 mol) to yield 0.21 g (97%) of (*S*)-**3**. An analytically pure sample of (*S*)-**3** was obtained by recrystallization from hexane. − M.p. 71.5−72.5°C. − $[\alpha]_D^{25}$ = − 550±10 (*c* = 0.4, C$_6$H$_6$). − C$_{18}$H$_{18}$O$_2$ (266.32): calcd. C 81.17, H 6.81; found C 81.47, H 6.61. − ^{1}H NMR data are identical to those of the racemic sample.

Synthesis of (*R*)-3 from (*R*)-1: The synthesis was carried out in accordance with the technique developed for the racemic compound, using (*R*)-**1** [0.031 g, 0.00014 mol, $[\alpha]_D^{20}$ = +7.12 (*c* = 1.1, CHCl$_3$)], TiCl$_4$ (0.02 mL, 0.034 g, 0.00018 mol) and acetyl chloride (0.01 mL, 0.011 g, 0.00014 mol), to yield 0.032 g (86%) of (*R*)-**3**. M.p. 71.5−72.5°C. − $[\alpha]_D^{25}$ = +510 (*c* = 0.4, C$_6$H$_6$). − C$_{18}$H$_{18}$O$_2$ (266.32): calcd. C 81.17, H 6.81; found C 81.00, H 7.11.

Synthesis of the Schiff Bases of Racemic 4 and (*S*)-α-PEA: To a solution of racemic **4** (0.624 g, 0.002 mol) in toluene (15 mL) (*S*)-α-PEA (0.73 mL, 0.69 g, 0.0057 mol) and TiCl$_4$ (0.21 mL, 0.36 g, 0.0019 mol) were added. The mixture was refluxed for 8 h in a flask equipped with a Dean−Stark trap filled with MgSO$_4$ and left overnight. The mixture, cooled to room temperature, was poured into a mixture of H$_2$O and ice and extracted with C$_6$H$_6$ (2 × 20 mL), the combined organic solutions were washed with H$_2$O (2 × 30 mL) and dried with Na$_2$SO$_4$. The solvent was evaporated in vacuo and the residue was passed through a short SiO$_2$ column with benzene as eluent. The orange fraction was concentrated to yield 0.749 g (91%) of a mixture of diastereomeric 4-hydroxy-5-[phenyl-(1-phenylethylimino)methyl][2.2]paracyclophane (*R*,*S*)- and (*S*,*S*)-**13** in equimolar ratio (according to ^{1}H NMR).

Separation of the Diastereomers (*S*,*S*)- and (*R*,*S*)-13: The mixture of diastereomeric (*R*,*S*)- and (*S*,*S*)-**13** (0.691 g) was recrystallized from 10 mL of EtOH to yield 0.103 g of enriched (*S*,*S*)-**13** as orange crystals. The filtrate was concentrated and the residue was recrystallized from 11 mL of MeOH to yield an additional portion (0.128 g) of enriched (*S*,*S*)-**13**. From the filtrate, 0.055 g of enriched (*R*,*S*)-**13** precipitated as a deep red crystals. The filtrate was concentrated and the residue was crystallized from 7 mL of MeOH to yield 0.084 g of enriched (*R*,*S*)-**13** as the first crop and 0.107 g of enriched (*S*,*S*)-**13** as the second crop. − Diastereomerically pure (*S*,*S*)-**13** (0.22 g, 73%) was obtained by final recrystallization of the combined orange material (0.34 g) from 17 mL of MeOH. − M.p.

183.5−184.5°C. − $[\alpha]_D^{25}$ = − 468 (*c* = 0.3, C_6H_6). − ^1H NMR ($CDCl_3$), δ = 1.47 (d, ^3J = 6.5 Hz, 3 H, C*H_3*), 1.65−1.75 (m, 1 H, −C*H*H−CH_2−), 2.11−2.27 (m, 2 H, −C*H*H−CH_2−), 2.54−2.65 (m, 1 H, −C*H*H−CH_2−), 2.69−2.80 (m, 1 H, −C*H*H−CH_2−), 3.01−3.12 (m, 1 H, −C*H*H−CH_2−), 3.21−3.32 (m, 1 H, −C*H*H−CH_2−), 3.49−3.59 (m, 1 H, −C*H*H−CH_2−), 4.69 (q, ^3J = 6.5 Hz, 1 H, α-*H*), 6.06 (d, ^3J = 7.8 Hz, 1 H, PC aromatic H^7 or H^8), 6.29 (d, ^3J = 7.8 Hz, 1 H, PC aromatic H^7 or H^8), 6.42−6.54 (m, 3 H, PC aromatic *H*), 7.11−7.22 (m, 1 H, PC aromatic *H* and 2 H, aromatic *H*), 7.32−7.58 (m, 8 H, aromatic *H*), 16.74 (s, 1 H, O*H*). − $C_{31}H_{29}NO$ (431.58): calcd. C 86.27, H 6.77; N 3.25, found C 86.36, H 6.83, N 3.15. − Diastereomerically pure (*R,S*)-**13** (0.11 g, 36%) was obtained after final crystallization of the combined deep red crystals (0.14 g) from 10 mL of EtOH. − M.p. 166.5−167.5°C. − $[\alpha]_D^{25}$ = +904 (*c* = 0.3, C_6H_6). − ^1H NMR ($CDCl_3$), δ = 1.68−1.78 (m, 1 H, −C*H*H−CH_2−), 1.84 (d, ^3J = 6.5 Hz, 3 H, C*H_3*), 2.20−2.29 (m, 1 H, −C*H*H−CH_2−), 2.35−2.47 (m, 1 H, −C*H*H−CH_2−), 2.49−2.59 (m, 1 H, −C*H*H−CH_2−), 2.82−2.92 (m, 1 H, −C*H*H−CH_2−), 2.98−3.07 (m, 1 H, −C*H*H−CH_2−), 3.18−3.28 (m, 1 H, −C*H*H−CH_2−), 3.43−3.53 (m, 1 H, −C*H*H−CH_2−), 4.84 (q, ^3J = 6.5 Hz, 1 H, α-*H*), 6.00 (d, ^3J = 7.8 Hz, 1 H, PC aromatic H^7 or H^8), 6.43 (d, ^3J = 7.8 Hz, 1 H, PC aromatic H^7 or H^8), 6.46 (d.d, ^3J = 7.8, ^4J = 1.8 Hz, 1 H, PC aromatic *H*), 6.51−6.57 (m, 2 H, PC aromatic *H*), 7.00−7.05 (m, 1 H, PC aromatic *H* and 1 H, aromatic *H*), 7.06−7.23 (m, 6 H, aromatic *H*),), 7.39−7.51 (m, 3 H, aromatic *H*), 16.46 (s, 1 H, O*H*). − $C_{31}H_{29}NO$ (431.58): calcd. C 86.27, H 6.77; N 3.25, found C 86.46, H 6.67, N 3.29.

Synthesis of (*R*)-4 from (*R*)-1: The acylation was carried out in accordance with the technique developed for the racemic compound, starting from (*R*)-**1** [0.040 g, 0.00018 mol, $[\alpha]_D^{20}$ = +7.12 (*c* = 1.1, $CHCl_3$)], $TiCl_4$ (0.026 mL, 0.044 g, 0.00023 mol), and benzoyl chloride (0.02 mL, 0.025 g, 0.00018 mol). After standard workup, the reaction mixture was passed twice through an SiO_2 column to yield 0.036 g (62%) of (*R*)-**4**. An analytically pure sample of (*R*)-**4** (0.026 g, 44%) was prepared by recrystallization from heptane. M.p. 151.5−152.5°C. − $[\alpha]_D^{25}$ = +250 (*c* = 0.24, C_6H_6) − $C_{23}H_{20}O_2$ (328.41): calcd. C 84.12, H 6.14; found C 83.64, H 6.59.

Synthesis of (*R,S*)-13 from (*R*)-4 and (*S*)-α-PEA: The synthesis was carried out in accordance with the technique developed for the reaction of racemic **4** and (*S*)-α-PEA, starting from (*R*)-**4** (0.012 g, 0.00004 mol), (*S*)-α-PEA (0.015 mL, 0.015 g, 0.00012 mol), and $TiCl_4$ (0.005 mL, 0.0076 g, 0.00004 mol). After standard workup and evaporation of the solvent in vacuo, the residue was passed through a short SiO_2 column with benzene as eluent to yield 0.016 g (98%) of (*R,S*)-**13**. M.p. 166.5−167.5°C. − $[\alpha]_D^{25}$ = +864 (*c* = 0.4, C_6H_6).

X-ray Crystallographic Study of (*R,S*)-13: Red crystals of the Schiff base were obtained by recrystallization from methanol. Crystal data: $C_{31}H_{29}NO$, FW = 431.55, red prisms, dimensions 0.35 × 0.20 × 0.15 mm, $d_{calcd.}$ = 1.231 g cm^{-1}, orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 9.1157(10) Å, *b* = 10.5261(12) Å, *c* = 24.264(3) Å, *V* = 2328.2(5) $Å^3$, *Z* = 4, *F*(000) = 920. A total of 7277 reflections were recorded with a Bruker SMART CCD area detector mounted on a 3-circle diffractometer [*T* = 110 K, graphite monochromator, λ(Mo-K_α) = 0.71073 Å, - and ω-scan techniques, no absorption correlation was applied, μ(Mo-K_α) = 0.073 mm^{-1}, Θ = 1.68−28.73°]. Of these, 5153 (R_{int} = 0.0614) independent reflections were used for structure solutions (SHELXTL Plus 5[19]). The structure was solved by direct methods, the non-hydrogen atoms were refined by full-matrix least-squares technique on F^2 in the anisotropic approximation. All hydrogen atoms were located in the difference Fourier syntheses and included in the refinement in the isotropic approximation. Final discrepancy factors: *R*1 = 0.0507 [on *F* for 4190 reflections with $I > 2\ \sigma(I)$], *wR*2 = 0.1279 (on F^2 for all 5153 reflections used in the refinement 414 parameters). GOOF = 0.977, largest difference peak and hole 0.302 and −0.222 e$Å^{-3}$. Atomic coordinates, full bond lengths and angles, and thermal parameters are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (deposition number CCDC-143745).

X-ray Crystallographic Study of (*S,S*)-13: Orange crystals of the Schiff base were obtained by crystallization from acetone. Crystal data: $C_{31}H_{29}NO$, FW = 431.55, orange prism, dimensions 0.1 × 0.2 × 0.4 mm, $d_{calcd.}$ = 1.247 g cm^{-1}, monoclinic, space group $P2_1$ (no. 4), *a* = 10.3115(6) Å, *b* = 20.2314(11) Å, *c* = 11.0228(6) Å, β = 90.843(1)°, *V* = 2299.3(2) $Å^3$, *Z* = 4, *F*(000) = 920. A total of 27604 reflections were recorded with a Bruker SMART CCD area detector mounted on a 3-circle diffractometer [*T* = 110 K, graphite monochromator λ(Mo-K_α) = 0.71073 Å, - and ω-scan techniques, no absorption correlation was applied, μ(Mo-K_α) = 0.074 mm^{-1}, Θ = 1.85−30.07°]. Of these, 13022 (R_{int} = 0.0512) independent reflections were used for structure solutions (SHELXTL Plus 5[19]). The structure was solved by direct method, the non-hydrogen atoms were refined by full-matrix least-squares technique on F^2 in the anisotropic approximation. All hydrogen atoms were located in the difference Fourier syntheses and included in the refinement in the isotropic approximation. Final discrepancy factors: *R*1 = 0.0484 [on *F* for 6801 reflections with $I > 2\ \sigma(I)$], *wR*2 = 0.0856 (on F^2 for all 12974 reflections used in the refinement 827 parameters). GOOF = 0.771, largest difference peak and hole 0.191 and −0.182 e$Å^{-3}$. Atomic coordinates, full bond lengths and angles, and thermal parameters are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (deposition number CCDC-143746).

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