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New chiral β-diketones based on [2.2]paracyclophane

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Abstract

Two chiral β-diketones, 1,3-bis[(*S*)-(4-[2.2]paracyclophanyl)]propane-1,3-dione (BPPD) and [1-(*S*)-(4-[2.2]paracyclophanyl)-3-phenyl]propane-1,3-dione (PPPD), were synthesized by acylation of (*S*)-4-acetyl-[2.2]paracyclophane with methyl esters from the corresponding carboxylic acids. 4-Acetyl[2.2]paracyclophane was synthesized in a quantitative yield by the reaction of [2.2]paracyclophane-4-carboxylic acid with methyllithium. © 1999 Elsevier Science Ltd. All rights reserved.

Only a few years ago the first attempts at the elaboration of chiral [2.2]paracyclophane derivatives as chiral auxiliaries in asymmetric synthesis were reported.[1–4] A number of chiral disubstituted paracyclophanes were found to be efficient as either chiral auxiliaries in stoichiometric asymmetric reactions[1,2] or chiral ligands in metal complex catalyzed asymmetric reactions.[3,4] Thus the asymmetric synthesis of α-aminoacids[2] and a catalytic trimethylsilylcyanation of benzaldehyde[3] with 5-formyl-4-hydroxy[2.2]paracyclophane [(*R*)- or (*S*)-FHPC, a chiral analogue of salicylaldehyde], as a source of asymmetric induction, were developed. Other types of ligands, 4,12-bis(diphenylosphino)-[2.2]paracyclophane [(*R*)- or (*S*)-[2.2]PHANEPHOS], were integrated into Ru- and Rh-complexes, which catalyzed hydrogenation reactions with high selectivity.[4a,c] It should be noted that all the chiral derivatives were constructed on the basis of a single [2.2]paracyclophanyl moiety with different locations for the functional groups either on one or two aromatic rings of the molecule (in *ortho*-, *pseudo-ortho*- or *pseudo-gem*-positions).

It was tempting to use [2.2]paracyclophane as a scaffold for the construction of a set of chiral 1,3-dicarbonyl compounds, a class of asymmetric inductors which have received little attention and rarely been used in asymmetric reactions.[5–7] A typical example of such compounds is presented by planar chiral β-diketones with C_2-symmetry. Recently, the first organometallic planar chiral β-diketone, 1,3-bis(2-methylferrocenyl)propane-1,3-dione [(*R*,*R*)-BMPD], was synthesized and a BMPD-yttrium complex

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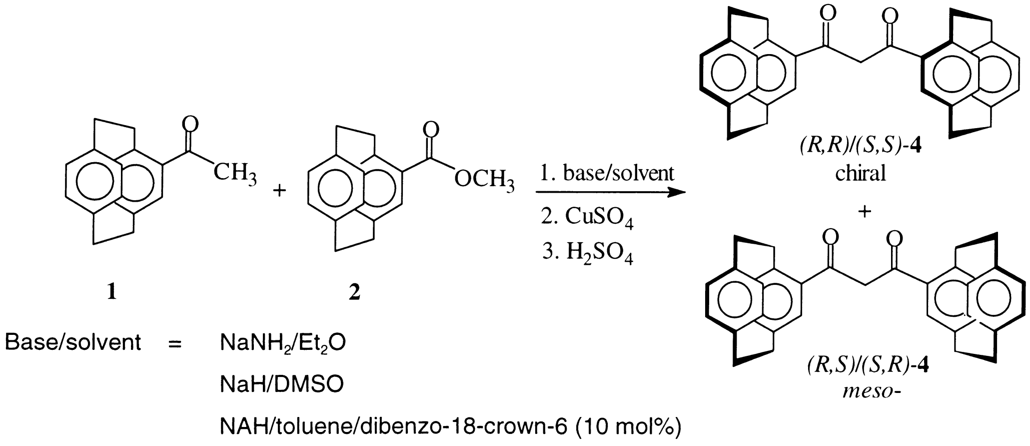
showed both high turnover of the catalyst and good enantioselectivity in the asymmetric silylcyanation of aldehydes.[8]

We believe that chiral β-diketones based on [2.2]paracyclophane might be effective chiral ligands in a range of asymmetric reactions (for example, Diels–Alder reactions[6] and cyclopropanations[7]) usually catalyzed by metal complexes with chiral diketonate ligands derived from camphor. The application of [2.2]paracyclphanyl β-diketonates of lanthanide metals as LIS-reagents for NMR spectroscopy[9] was also envisaged.

For the synthesis of β-diketones the acylation reaction[10] of 4-acetyl[2.2]paracyclophane **1** with 4-methoxycarbonyl[2.2]paracyclophane **2** was chosen. Our choice was conditioned by the fact that both paracyclophane derivatives **1** and **2** could be obtained in enantiomerically pure forms from the readily available enantiomerically pure [2.2]paracyclophane-4-carboxylic acid **3**. The procedure for the synthesis and resolution of **3** has recently been improved.[11] The protocol included successive lithiation–carboxylation of 4-bromo[2.2]paracyclophane to give racemic **3** which was resolved via diastereomeric α-(*p*-nitrophenyl)ethylammonium salts.[11] Scale-up of the resolution procedure from 0.5 to 2 g was more efficient and both enantiomers of **3** were obtained with higher enantiomeric excess than previously reported,[11] after a single crystallization of the salt from EtOH [(*S*)-**3**: $[\alpha]_D^{25}$ +172 and (*R*)-**3**: $[\alpha]_D^{25}$ −173 (lit.[13] $[\alpha]_D^{25}$ +170 and $[\alpha]_D^{25}$ +175].[12]

Compound (*S*)-**1** was synthesized in a quantitative yield by treatment of (*S*)-**3** with 2 equiv. of methyllithium in Et_2O.[14] Racemic **1** was synthesized using the procedure given by Cram and Allinger.[15] For the synthesis of racemic **2** and (*S*)-**2** the initial acylchlorides were obtained from the corresponding acid **3** followed by treatment with MeOH.

Acylation reaction of ketone **1** with ester **2** was initially carried out with the racemic starting materials (Scheme 1). Several base:solvent combinations were compared with this reaction. A molar ratio of base to **2** and **1** was chosen as 2:2:1. When $NaNH_2$ was used as a base in Et_2O after 2 h, only a trace of the target product was detected in the reaction mixture by TLC. The 1,3-bis[(4-[2.2]paracyclophanyl)]propane-1,3-dione, (BPPD) **4** was obtained in a yield of 10% when DMSO and NaH were used as a solvent and a base, respectively, and the reaction was carried out for 2 h. From the reaction mixture **4** was isolated as a copper complex. Finally, the β-diketone was regenerated from the complex and analyzed. ^1H NMR analysis showed that chiral-[(*R*,*R*):(*S*,*S*)] and *meso*-isomers [(*R*,*S*):(*S*,*R*)] were formed in a 1:1 ratio.

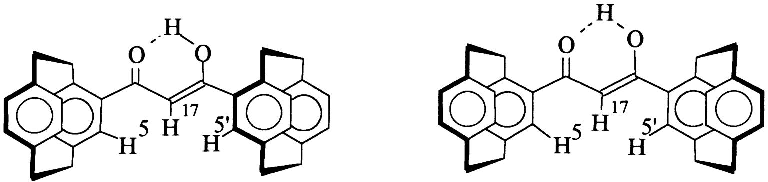


Scheme 1.

In an attempt to increase the yield of **4** reaction time was prolonged to 9 h. However, the recovery of the copper complex and its decomposition, after work-up of the reaction mixture, isolated a by-product (of undetermined structure) containing sulfur together with the target **4**. β-Diketone was separated from the by-product by column chromatography (SiO_2) with a chemical yield of 12%. Under the same conditions, the reaction with optically active starting materials was carried out and (*S*,*S*)-**4** obtained in a 14% yield. The performance of condensation was further improved [yield of **4** was 22%] by carrying the reaction out in toluene in the presence of a phase transfer catalyst (crown ether), as suggested earlier for the synthesis of sterically congested diketones.[16]

In all the experiments the initial 4-acetyl[2.2]paracyclophane was recovered unchanged from the reaction mixture in a 60–65% yield.

^1H NMR spectra for the single diastereoisomer (*S*,*S*)-**4** was recorded. By addition of a 1:1 mixture of racemic **4** and *meso*-**4** to a solution of (*S*,*S*)-**4** in $CDCl_3$ the location of the signals for diastereotopic protons in the ^1H NMR spectra for chiral- and *meso*-isomers was defined (Scheme 2). The signals of diastereotopic protons at 6.12 and 6.14, 6.92 and 6.89, 16.87 and 16.92 were attributed to H^{17}, H^5 and OH resonances, correspondingly (Scheme 2). The presence of sharp singlets of H^{17} and the OH-group, together with a significant downfield shift of the latter, unambiguously indicated that both diastereoisomers of **4** existed in the solutions predominantly as enols with a strong intramolecular hydrogen bond.

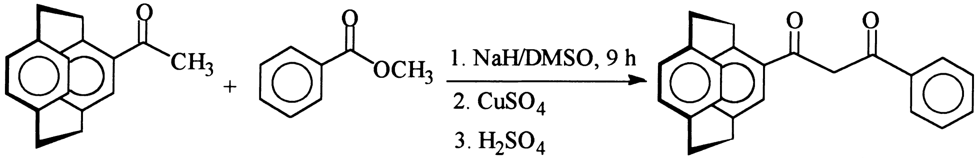


(S,S) (or (R,R))-**4** *meso*-**4**

$\delta_{H}17$ 6.12 ppm $\delta_{H}17$ 6.14 ppm
$\delta_{H}5/5'$ 6.92 ppm $\delta_{H}5/5'$ 6.89 ppm
δ_{OH} 16.87 ppm δ_{OH} 16.92 ppm

Scheme 2.

We presumed that the low yield of symmetrical β-diketone **4** in the condensation reaction could be ascribed to unfavorable steric effects, resulting from the presence of bulky [2.2]paracyclophanyl substituents at the carbonyl groups of both reagents. In order to minimize the steric hindrance in the transition state of the reaction, the acylation of racemic or (*S*)-**1** with methylbenzoate **5** in DMSO with NaH as a base (molar ratio of base to **5** to **1** was 2:2:1) was carried out (Scheme 3). As expected, the synthesis of the unsymmetric β-diketone went to completion to give [1-(4-[2.2]paracyclophanyl)-3-phenyl]propane-1,3-dione (PPPD) **6** with no starting 4-acetyl[2.2]paracyclophane detected in the reaction mixture. The racemic sample was extracted in a Soxhlet apparatus with toluene to yield 53% of **6**. The optically active sample was purified by column chromatography to yield 62.5% of (*S*)-**6**. ^1H NMR spectra of (*S*)-**6** showed that all proton resonances, in particular those of OH and CH= protons and H5, appear in a similar fashion for (*S*,*S*)-**4** and (*S*)-**6**.



rac- or *(S)*-**1** **5** *rac-* or *(S)*-**6**

Scheme 3.

1. Conclusion

The first chiral β-diketone derivatives of [2.2]paracyclophane, 1,3-bis[(*S*)-(4-[2.2]paracyclophanyl)]-propane-1,3-dione (BPPD) and 1-[4-(*S*)-(4-[2.2]paracyclophaniyl)-3-phenyl]propane-1,3-dione (PPPD), were synthesized by the acylation reaction of (*S*)-4-acetyl[2.2]paracyclophane with methyl esters of the corresponding carboxylic acids in the presence of bases. Although the conditions of the condensation reaction were not optimized, there is no doubt that the chemical yields of the diketones can be increased significantly. The development of the reaction is still ongoing. The complexation ability of the β-diketones was demonstrated by means of copper(II) chelate formation. Studies on the application of the chiral diketones as ligands for metal complex catalysts of asymmetric reactions are underway.

2. Experimental section

2.1. General

^{1}H NMR spectra were recorded on a Bruker AMX-400 instrument (400.13 MHz) with $CHCl_3$ (δ=7.27 ppm) as an internal standard. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a thermostated cell at 25°C. TLC analyses were performed on silica gel precoated plates ‘Silufol UV-254’ (Chemapol). Column chromatography was performed on Kieselgel 60 (Merck).

Et_2O was distilled from benzophenone ketyl under argon prior to use. Toluene was distilled from potassium metal prior to use. DMSO was kept under KOH at 60°C and then distilled at 55–56°C/4 mmHg.

2.2. (+)-(S)- and (−)-(R)-[2.2]Paracyclophane-4-carboxylic acid **3**

The previously described resolution procedure[11] was scaled up to 2.0 g of racemic **3**. The diastereoisomeric (*S*,*S*)-salt of **3** with (*S*)-α-(*p*-nitrophenyl)ethylamine was prepared using the procedure[11] and additionally recrystallized from EtOH to yield after hydrolysis (*S*)-**3** with $[\alpha]_D^{25}$ +172 (c=0.5, $CHCl_3$), (lit.[13] $[\alpha]_D^{25}$ +170 (c=0.5, $CHCl_3$)). Diastereoisomeric (*R*,*R*)-α-(*p*-nitrophenyl)ethylammonium salt derived from the partially resolved (*R*)-**3**, [recovered from the mother liquor of the resolution of racemic **3** with (*S*)-α-(*p*-nitrophenyl)ethylamine] after a single crystallization from EtOH and hydrolysis gave (*R*)-**3** with $[\alpha]_D^{25}$ −173 (c=0.5, $CHCl_3$); an improvement on $[\alpha]_D^{25}$ −159.2 (c 0.5 $CHCl_3$) reported by us previously[11] (lit.[13] $[\alpha]_D^{25}$ −175 (c=0.68, $CHCl_3$)).

2.3. Racemic 4-acetyl[2.2]paracyclophane **1**

Racemic 4-acetyl[2.2]paracyclophane **1** was synthesized according to the procedure by Cram and Allinger.[15] M.p. 108–109°C (lit.[15] 109.7–110.4°C).

2.3.1. (+)-(S)-4-Acetyl[2.2]paracyclophane (S)-**1**

A solution of MeLi (7.2 mL of a 0.735 M solution in Et_2O, 5 mmol) was added to a solution of (*S*)-[2.2]paracyclophane-4-carboxylic acid (*S*)-**3** (0.52 g, 2.1 mmol) in 30 mL of Et_2O. The mixture was stirred at room temperature for 10 min, then refluxed for 7 h and kept at room temperature overnight. The mixture was then vigorously stirred with H_2O for 0.5 h, the layers separated and the aqueous solution extracted with Et_2O (3×25 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated to yield 0.5 g (96%) of a crude product. Recrystallization of this material from heptane (10 mL) yielded 0.37 g (72%) of analytically pure (*S*)-**1**. M.p. 130.5–131°C, $[\alpha]_D^{25}$=+65.4 (c=0.4, $CHCl_3$), (lit. m.p. 120–124°C, $[\alpha]_D^{25}$=+65 (c=0.5, $CHCl_3$[14a,b]); m.p. 127–128°C, $[\alpha]_D^{25}$=−65 (c=1.0, $CHCl_3$[14c]).

*2.4. 4-Methoxycarbonyl[2.2]paracyclophane **2***

$SOCl_2$ (0.87 mL; 1.42 g, 11.9 mmol) was added to a suspension of 0.65 g (2.58 mmol) of **3** in 11 ml of C_6H_6, the mixture was refluxed for 75 min and cooled to room temperature. To this solution of the resultant acylchloride, 25 mL MeOH was added dropwise under vigorous stirring. The reaction mixture was evaporated to dryness and the crude product (0.69 g) was purified by column chromatography to yield 0.61 g (88%) of **2**. The analytically pure sample (0.52 g, 75%) was obtained by crystallization of this material from EtOH. M.p. 137–138°C (lit. m.p. 139–140°C,[17a] m.p. 135–138°C[17b]).

*2.4.1. (S)-4-Methoxycarbonyl[2.2]paracyclophane (S)-**2***

(*S*)-4-Methoxycarbonyl[2.2]paracyclophane (*S*)-**2** was obtained using the procedure described above, from 0.6 g (2.4 mmol) of (+)-(*S*)-**3** with 88% yield (0.5 g). M.p. 171–172°C, $[\alpha]_D^{25}$=+156.4 (c=0.55, $CHCl_3$) (lit. m.p. 174–175°C, $[\alpha]_D^{25}$=−151.3 (c=1.2, $CHCl_3$),[18] m.p. 172–175°C, $[\alpha]_D^{25}$=−153 (c=0.5, $CHCl_3$)[13]).

*2.5. General procedure for the acylation of 4-acetyl[2.2]paracyclophane **1** with 4-methoxycarbonyl[2.2]paracyclophane **2***

Compound **2** (0.28 g, 1.0 mmol) was added to a suspension of NaH (0.032 g, 1.0 mmol) in DMSO (6 mL) under argon. After stirring for 5 min a solution of **1** (0.13 g, 0.5 mmol) in DMSO (3 mL) was added by syringe and the reaction mixture stirred for 2 h (or 9 h), keeping the bath temperature at 60°C. The mixture was left overnight, then poured into ice and water (50 mL) containing conc. HCl (50 mL). After separation of the layers the aqueous solution was extracted with Et_2O (3×25 mL), $CHCl_3$ (3×25 mL), and combined organic fractions washed with $NaHCO_3$ (3×25 mL) and H_2O (3×25 mL). The organic solution was poured into a copper acetate solution, then methanol (30 mL) was added and the mixture stirred at room temperature for 12 h. The copper chelate was precipitated as a bright greenish-blue powder. The chelate was decomposed by stirring with a mixture of 40 mL of 10% aq. H_2SO_4 (20 mL) and Et_2O (20 mL), the organic layer was washed with $NaHCO_3$ (3×25 mL) followed by H_2O (3×25 mL) and dried over Na_2SO_4. Racemic 1,3-bis[(4-[2.2]paracyclophanyl)]propane-1,3-dione (BPPD), **4** (0.05 g, 10% for 2 h reaction) was obtained after the hydrolysis of the copper complex. ^1H NMR ($CDCl_3$): δ=2.9–3.3 (m, 14H, CH_2–CH_2), 3.95 (m, 2H, C*H*H–CH_2), 6.12 and 6.14 (s, 1H, H^{17}), 6.45–6.78 (m, 12H), 6.88 and 6.92 (d, *J*=2.0 Hz, 2H, $H^5/H^{5'}$), 16.87 and 16.93 (s, 1H, O*H*). M.p. 236–238°C.

*2.5.1. 1,3-Bis[(S)-(4-[2.2]paracyclophanyl)]propane-1,3-dione (S,S)-**4***

This preparation was synthesized in accordance with same procedure as given above, starting from (*S*)-**2** (0.28 g, 1.0 mmol), NaH (0.032 g, 1.0 mmol) and (*S*)-**1** (0.13 g, 0.5 mmol), reaction time 9 h. After decomposition of the copper complex all the fractions containing (*S*,*S*)-**4** were combined and evaporated. The column chromatography (SiO_2, benzene) gave 0.067 g (14%) of (*S*,*S*)-**4**, 0.02 g of by-product and 0.083 g (64%) of starting ketone (*S*)-**1**. Analytically pure (*S*,*S*)-**4** was obtained by crystallization from EtOH. M.p 267–268°C. Found: C, 87.10; H, 6.63%. $C_{35}H_{32}O_2$ required C, 86.74; H 6.66%. $[\alpha]_D^{25}$=+210 (c=0.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ=2.9–3.3 (m, 14H, CH_2–CH_2), 3.95 (m, 2H, C*H*H–CH_2), 6.13 (s, 1H, H^{17}), 6.47 (d.d, *J*=2.0 Hz, *J*=7.8 Hz, 2H), 6.54–6.68 (m, 8H), 6.70 (d.d, *J*=2.0 Hz, *J*=7.8 Hz, 2H), 6.90 (d, J=2.0 Hz, 2H, H^5/H^5), 16.85 (s, 1H, OH). MS (70 eV); m/z (%) 484 [M]+ (26), 467 (20); 131 (100), 104 (50). IR (KBr): ν=1610 cm^{-1} (C=O).

2.6. *Acylation of* ***1*** *with* ***2*** *in the presence of 10% dibenzo-18-crown-**6***

A solution of ketone **1** (0.15 g, 0.6 mmol) in toluene (1.5 mL) and a suspension of dibenzo-18-crown-6 (0.021 g, 0.06 mmol) in toluene (3 mL) were successively added to a mixture of **2** (0.319 g, 1.2 mmol) and NaH (0.06 g, 1.2 mmol) in toluene (1.5 mL) in an argon atmosphere. The reaction mixture was stirred for 22 h after reflux. The reaction mixture was then poured into 10% H_2SO_4, and after separation of the layers the aqueous solution was extracted with Et_2O (3×25 mL), combined organic fractions washed with $NaHCO_3$ (3×25 mL) and H_2O (3×25 mL), dried over $MgSO_4$ and the solvent evaporated. Column chromatography of the solid residue (0.334 g) with benzene as an eluent yielded 0.65 g (22%) of **4**, 0.23 g (16%) of **1** and 0.63 g (42%) of **2**.

2.7. *Acylation of 4-acetyl[2.2]paracyclophane* ***1*** *with methyl benzoate* ***5***

Compound 5 (0.56 g, 0.5 mL, 4 mmol) was added by syringe to a suspension of NaH (0.14 g, 4 mmol) in DMSO (20 mL). After stirring for 5 min a solution of **1** (0.5 g, 2 mmol) in DMSO (8 mL) was added by syringe and the reaction mixture was stirred for 0.5 h at room temperature and then for 9 h keeping the bath temperature at 60°C. The reaction mixture was worked up, as described above. The yield of the copper chelate was 0.244 g (28%), it was hydrolyzed to give 0.18 g (24%) of β-diketone. All the fractions containing **6** were combined and evaporated. The crude product (0.61 g, 88%) was extracted in a Soxhlet apparatus with toluene for 50 min to yield 0.375 g (53%) [1-(4-[2.2]paracyclophanyl)-3-phenyl]propane-1,3-dione (PPPD) **6**. The analytically pure **6** was obtained in a 45% yield by crystallization from the EtOH:toluene mixture (9:1, 50 mL). M.p. 174–175°C. Found: C, 84.83; H, 6.39%. $C_{25}H_{22}O_2$ C, 84.71; H, 6.26%.

2.7.1. *[1-(*S*)-(4-[2.2]Paracyclophanyl)-3-phenyl]propane-1,3-dione (*S*)-**6***

This preparation was obtained according to the procedure described above, starting from **5** (0.28 g, 0.25 mL, 2 mmol), NaH (0.07 g, 2 mmol) and (*S*)-**1** (0.25 g, 1 mmol). The crude product (0.286 g, 76%) was purified by column chromatography (SiO_2, benzene) to yield 0.225 g of (*S*)-**6** (62.5%). An analytically pure sample was obtained in 35% yield by crystallization from EtOH:toluene mixture (9:1, 7.8 mL). M.p. 102–103°C. Found: C, 84.84; H, 6.29%. $C_{25}H_{22}O_2$ C, 84.71; H, 6.26%. $[\alpha]_D^{25}$=+145.2 (c=0.6, toluene). ^{1}H NMR ($CDCl_3$): δ=2.9–3.35 (m, 7H, CH_2–CH_2), 3.95 (m, 1H, CHH–CH_2), 6.48 (s, 1H, H^{17}), 6.45–6.70 (m, 6H, arom. paracycl. H), 6.95 (d, J=2.0 Hz, 1H, arom. paracycl. $H^5/H^{5'}$), 7.45–7.60 (m, 3H, arom. Ph *m*- and *p*-*H*), 7.97 (d, J=8.0 Hz, 2H, arom. Ph *o*-*H*), 16.8 (bs, 1H, OH). MS (70 eV); *m/z* (%): 352 (10) [M^+], 337 (13), 176 (100), 160 (85), 145 (15). IR (KBr): <=1610 cm^{-1} (br.), 1565 cm^{-1}.

Acknowledgements

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