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Improved Synthesis of (±)-4,12-Dihydroxy[2.2]paracyclophane and Its Enantiomeric Resolution by Enzymatic Methods: Planar Chiral (*R*)- and (*S*)-Phanol

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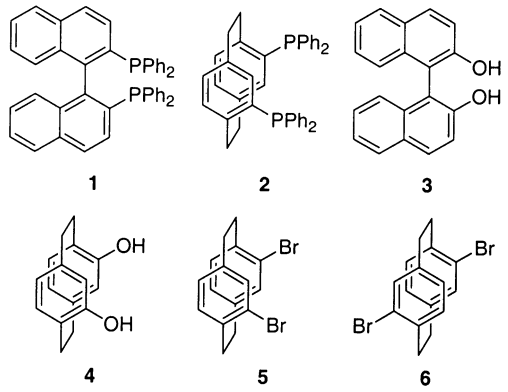
Abstract: (±)-4,12-Dihydroxy[2.2]paracyclophane [(±)-PHANOL] is readily prepared from [2.2]paracyclophane by an improved synthetic protocol. Enzymatic kinetic resolution of its bis-acetate proceeds with good enantioselection. Separation, hydrolysis, and recrystallization provides both enantiomers of PHANOL in high enantiopurity.

Enantiopure ligands retain an important position in current chemical research.[1] For example, axially chiral (*R*)- or (*S*)-BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] **1**[2] bestride the field of asymmetric catalysis as chelating bisphosphine ligands on a variety of metal centers.[3,4] Recently, 4,12-bis(diphenylphosphino)[2.2]-paracyclophane (PHANEPHOS) **2** was introduced as a chelating bisphosphine, chiral due to planar chirality,[5] and was shown to be an excellent ligand on rhodium for catalytic asymmetric hydrogenation,[6] on palladium for kinetic resolution via catalytic amination,[7] and on ruthenium for the catalytic asymmetric hydrogenation of β-ketoesters[8] or aromatic, heteroaromatic, and α,β-unsaturated ketones.[9] In all these cases, the PHANEPHOS ligand is at least comparable in its performance compared to BINAP. It is clear that the axial and planar chirality expressed by the 1,1′-binaphthyl and the [2.2]-paracyclophane[10] units, respectively, in these bisphosphines are powerful stereocontrolling elements. Since axially chiral BINOL (1,1′-binaphthyl-2,2′-diol) **3** is the prototypical chelating diol for oxophilic metals for myriad catalytic asymmetric transformations, including the glyoxylate ene reaction,[11] allylation of aldehydes[12] and ketones,[13] Michael reactions,[14] the aldol reaction,[15] and Diels−Alder reactions[16] we were drawn to investigate the synthesis and resolution of its planar chiral [2.2]paracyclophane analogue: 4,12-dihydroxy[2.2]paracyclophane (**4**), which we have dubbed "PHANOL".



In his pioneering work on paracyclophanes, Cram described (±)-diol **4** as early as 1969.[17] However, to the

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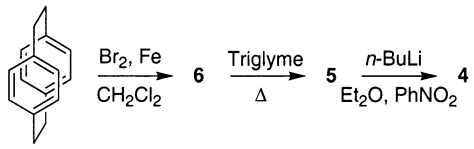
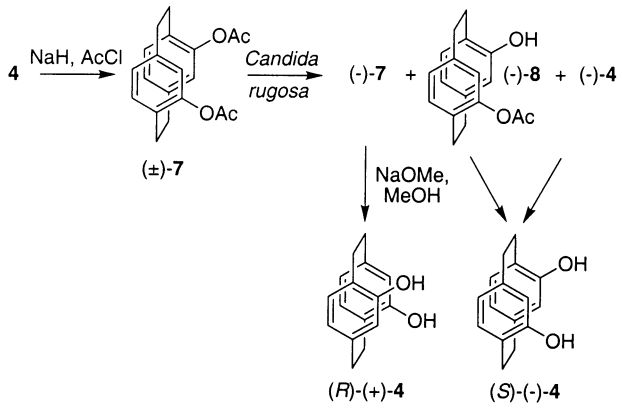
SCHEME 1



SCHEME 2

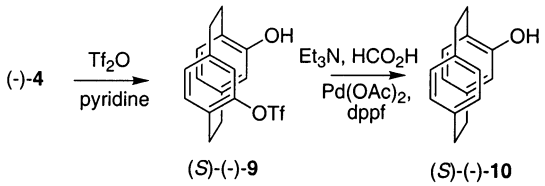


best of our knowledge, the resolved enantiomers of PHANOL **4** have not yet been reported. Cram's route involved bromination of [2.2]paracyclophane to give a mixture of all possible dibromo compounds, from which the 4,12-dibromo[2.2]paracyclophane (**5**) could be isolated after lengthy and extensive purification (15.7%). Double bromine−lithium exchange followed by an oxidative quench (nitrobenzene) provided (±)-diol **4** in low yield (16%), which was characterized as its dimethyl ether. More recently, it has been shown that dibromide **5** is obtained more conveniently via thermal isomerization of 4,16-dibromo[2.2]paracyclophane (**6**), itself obtained as the major product in the dibromination of [2.2]paracyclophane.[6] We have now combined these procedures and, with several key modifications, are able to access (±)-PHANOL **4** in three steps from commercially available [2.2]paracyclophane. We also disclose an enzymatic kinetic resolution method that allows access to both (*R*)- and (*S*)-PHANOL with high enantiomeric purity.

Our route to racemic PHANOL **4** is based on that of Cram[17] and the more recent route of Pye and Rossen[6] but with several key modifications (Scheme 1). Bromination of [2.2]paracyclophane using dichloromethane as a solvent rather than carbon tetrachloride results in the crystallization of essentially pure 4,16-dibromide **6** from the reaction mixture upon cooling (38%). The ensuing thermal isomerization step utilizes a modified workup procedure to isolate pure 4,12-dibromide **5** (37%). Dilithiation−oxidative quench on dibromide **5** in tetrahydrofuran solvent gives a much improved yield of (±)-PHANOL **4** (35−45%) compared to the originally reported yield (16%) when performed in diethyl ether.

The resolution of (±)-PHANOL **4** was achieved using the commercially available lipase *Candida rugosa* as a hydrolase for kinetic resolution of [2.2]paracyclophane-4,12-bisacetate (**7**) (Scheme 2). After 14 days, an approximate 2:1:1 mixture of unreacted bisacetate (−)-**7**, monoacetate (−)-**8**, and diol (−)-**4** results. Separation of the bisacetate (−)-**7** from the monoacetate (−)-**8** and diol (−)-**4** proved to be possible by column chromatography. Ester hydrolysis of acetate (−)-**7** gave rise to diol **4** with a positive specific rotation. Mixed solvent recrystallization (ethanol/water) gave (+)-PHANOL **4** essentially as a single enantiomer (36%, 98% ee). Ester hydrolysis of the monoacetate/diol mixture produced diol **4** with a negative specific rotation. Recrystallization as before produced (−)-PHANOL **4** (29%, >98% ee).

SCHEME 3



The configurations of the enantiomerically pure PHANOLS were assigned by transformation into a [2.2]paracyclophane of known configuration (Scheme 3). (−)-PHANOL **4** was allowed to react with triflic anhydride in pyridine to give (−)-hydroxytriflate **9** (43%). Palladium-catalyzed reduction of monotriflate **9** produced the known 4-hydroxy[2.2]paracyclophane (**10**). This compound displayed a negative optical rotation ($[\alpha]^{24}_D$ −8.3° (*c* 1.20, $CHCl_3$)). Comparison with the literature indicated that this corresponds to the (*S*)-configuration.[18] Therefore, (−)-PHANOL **4** obtained through selective hydrolysis from racemic bisacetate **7** using the lipase *Candida rugosa* exists as the (*S*)-configuration also, and it follows that the unreacted (−)-acetate **7** gives rise to (*R*)-(+)-PHANOL upon hydrolysis. Interestingly, the use of *Candida rugosa* for the enzymatic hydrolysis using a diethyl ether cosolvent of the structurally similar *monosubstituted* 4-acetoxy[2.2]paracyclophane is reported to preferentially hydrolyze the (*R*)-acetate to produce the (*R*)-configured 4-hydroxy[2.2]paracyclophane **10** ($[\alpha]^{24}_D$ +7.9° (*c* 1.13, $CHCl_3$)).[18] This is in striking contrast with our *disubstituted* paracyclophane **7** where the (*S*)-acetate is preferentially hydrolyzed to give the (*S*)-diol **4**. To eliminate the possibility that different commercial sources of *Candida rugosa*[19] were responsible for this effect, hydrolysis experiments on racemic monoacetoxy[2.2]paracyclophane[18] with our *Candida rugosa* enzyme source were performed with either diethyl ether or toluene as cosolvents. The (*R*)-hydroxy compound **10** was produced in both cases [from Et_2O, 52% $[\alpha]^{24}_D$ +7.7 (*c* 1.22, $CHCl_3$); from PhMe, 41% $[\alpha]^{24}_D$ +7.5° (*c* 1.13, $CHCl_3$)]. Finally, subjecting (+)-PHANOL **4** to the same triflation/reduction sequence as for (−)-PHANOL **4** in Scheme 3 resulted in 4-hydroxy[2.2]paracyclophane (**10**) with a positive optical rotation ($[\alpha]^{24}_D$ +8.6° (*c* 1.13, $CHCl_3$)), thus unambiguously confirming the (*R*)-configuration assignment for (+)-PHANOL.

In conclusion we have shown that both hands of 4,12-dihydroxy[2.2]paracyclophane (PHANOL) **4** can be obtained via enzymatic kinetic resolution. Their absolute

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stereochemistries were assigned by correlation with a paracyclophane of known configuration. These resolved 4,12-dihydroxy[2.2]paracyclophanes should find application as chiral control elements in asymmetric catalysis and in other areas of asymmetric synthesis.

Experimental Section

General. All reactions, except the kinetic resolution of (±)-**7**, were performed in oven-dried glassware under an atmosphere of N_2. THF was distilled from K/Ph_2CO. DMF and nitrobenzene were distilled from CaH_2. AcCl, pyridine, and NEt_3 were distilled immediately before use. *n*-Butyllithium was titrated against propan-2-ol/phenanthroline directly before use. All other chemicals were used as received.

Chromatographed refers to column chromatography performed on BDH silica gel 60, 230−400 mesh ASTM (eluants are given in parentheses). Concentrated refers to concentrated in vacuo. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualized with ultraviolet light (254 nm) or potassium permanganate as appropriate. Chiral HPLC analysis was performed on a Chirapack-AD column using 15% EtOH in hexane as an eluent detecting at 310 nm.

(±)-4,12-Dihydroxy[2.2]paracyclophane (4). *n*-Butyllithium (53.4 mL, 2.5 M, 134 mmol) was added slowly to a solution of 4,12-dibromo[2.2]paracyclophane **5** (see Supporting Information) (11.64 g, 31.8 mmol) in THF (320 mL) at −78 °C. The solution was allowed to warm to room temperature and then recooled to −78 °C, and $PhNO_2$ (13.0 mL, 127 mmol) was added. The mixture was allowed to warm to room temperature, and the reaction was quenched with aqueous HCl (2.0 M, 60 mL). The volatile solvents were removed in vacuo, and aqueous NaOH (2.0 M, 200 mL) and CH_2Cl_2 (200 mL) were added. The organic layer was separated and the aqueous layer washed with CH_2Cl_2, acidified with HCl, and extracted with EtOAc. The combined EtOAc layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, concentrated, and chromatographed (4:1 hexane/EtOAc) to give diol (±)-**4** (3.42 g, 45%) as a light tan solid: TLC R_f 0.29 (2:1 hexane/EtOAc); mp 221−225 °C; IR (DRIFTS) 3352 cm^{-1}; ^1H NMR (DMSO, 300 MHz) δ 2.36−2.51 (2H, m), 2.69−2.85 (4H, m), 3.17−3.26 (2H, m), 5.97 (2H, dd, J = 7.7, 1.5 Hz), 6.11 (2H, d, J = 1.5 Hz), 6.29 (2H, d, J = 7.7 Hz), 8.48 (2H, s); ^{13}C NMR (DMSO, 75 MHz) 31.4, 33.6, 118.3, 123.8, 124.9, 135.6, 142.1, 155.8; *m*/*z* (EI) 240 (M^+); HRMS (EI) calcd for $C_{16}H_{16}O_2$ 240.1150, found 240.1151. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.96; H, 6.74.

(±)-[2.2]Paracyclophane-4,12-bisacetate (7). NaH (60% suspension in mineral oil, 148 mg, 3.68 mmol) was added to a stirred solution of (±)-diol **4** (295 mg, 1.23 mmol) in THF (3 mL) at room temperature. The mixture was stirred for 1 h, acetyl chloride (0.44 mL, 6.15 mmol) was added and the reaction mixture stirred for 1 h. The mixture was poured into aqueous HCl (2 M, 20 mL) and extracted with EtOAc, and the combined organics were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed (CH_2Cl_2) to give bisacetate **7** (356 mg, 90%) as a white crystalline solid: TLC R_f 0.25 (CH_2Cl_2); mp 145−148 °C; IR (DRIFTS) 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.32 (6H, s), 2.61−2.72 (2H, m), 2.89−3.18 (6H, m), 6.42 (2H, dd, J = 7.8, 1.6 Hz), 6.46 (2H, d, J = 1.6 Hz), 6.54 (2H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 21.3, 31.5, 33.5, 124.4, 130.6, 130.8, 135.4, 141.8, 149.0, 169.0; *m*/*z* (EI) 324 (M^+); HRMS (EI) calcd for $C_{20}H_{20}O_4$ 324.1362, found 324.1359. Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 74.02; H, 6.31.

Enzymatic Resolution of (±)-[2.2]Paracyclophane-4,12-bisacetate (7). A solution of (±)-bisacetate **7** (2.0 g, 6.18 mmol) in PhMe (80 mL) was added to a solution of the lipase *Candida rugosa* (2.4 kU/g, 2.0 g) in a pH 7 aqueous phosphate buffer solution (0.05 M, 130 mL) prepared at room temperature. The biphasic mixture was heated to 40 °C for 14 days, allowed to cool to room temperature, and evaporated. The crude solid was triturated with EtOAc (3 × 50 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated to give a mixture of **7**, monoacetate **8**, and diol **4** (ca. 2:1:1 by ^1H NMR analysis). The mixture was chromatographed (CH_2Cl_2/2% MeOH in CH_2Cl_2) to give first (*R*)-(−)-bisacetate **7** (0.956 g, 48%) as a pale yellow solid: mp 152−155 °C; $[\alpha]^{24}_D$ −1.6° (*c* 1.0, $CHCl_3$), 87% ee by HPLC analysis after hydrolysis to resulting diol **4**. Second, (*S*)-(−)-monoacetate **8** (135 mg, 7.7%) was obtained as a white solid: TLC (CH_2Cl_2) R_f 0.15; mp 155−156 °C; $[\alpha]^{24}_D$ −36.6° (*c* 1.0; $CHCl_3$), 97% ee by HPLC analysis after hydrolysis to resulting diol **4**; IR (KBr plates) 3333, 1723 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.32 (3H, s), 2.54−2.78 (2H, m), 2.85−2.94 (2H, m), 3.01−3.15 (3H, m), 3.35−3.44 (1H, m), 5.58 (1H, s), 5.80 (1H, d, J = 1.6 Hz), 6.25 (1H, dd, J = 7.8, 1.6 Hz), 6.28 (1H, dd, J = 7.8, 1.6 Hz), 6.45 (1H, d, J = 7.8 Hz), 6.51 (1H, d, J = 7.8 Hz), 6.79 (1H, d, J = 1.6 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) 21.5, 30.4, 31.2, 33.3, 33.7, 119.7, 121.1, 124.9, 126.4, 129.5, 131.2, 134.9, 135.4, 141.8, 142.0, 149.1, 154.4, 169.9; *m*/*z* (EI) 282 (M^+); HRMS (EI) calcd for $C_{18}H_{18}O_3$ 282.1256, found 282.1255. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.52; H, 6.48. Finally, a mixture of (*S*)-(−)-**8** and (*S*)-(−)-**4** (633 mg) was obtained. This mixture was hydrolyzed to give (*S*)-(−)-**4** (608 mg, 41%) as a yellow solid: 87% ee by HPLC analysis. The pure monoacetate **8** was also hydrolyzed to give (*S*)-(−)-**4**. The combined (*S*)-(−)-**4** was recrystallized (EtOH, H_2O) to give enantiopure (*S*)-(−)-**4** (430 mg, 29%) as a white solid: mp 229−231 °C; $[\alpha]^{24}_D$ −92.4° (*c* 1.0, EtOH); >98% ee by HPLC analysis. (*R*)-(−)-Bisacetate **7** was hydrolyzed and recrystallized (EtOH, H_2O) to give (*R*)-(+)-**4** (540 mg, 36%) as a yellow solid: mp 228−231 °C, $[\alpha]^{24}_D$ +95.4° (*c* 1.0, EtOH); 98% ee by HPLC analysis.

General Hydrolysis Procedure for [2.2]Paracyclophane Actetates. To a stirred solution of [2.2]paracyclophane acetate in methanol was added finely ground sodium hydroxide (20 equiv). The mixture was heated to reflux for 10 min, cooled to room temperature, poured into aqueous HCl, diluted with water, and extracted with EtOAc. The combined organic layers were washed consecutively with $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated.

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Supporting Information Available: Improved experimental procedures for the preparation of dibromo[2.2]paracyclophanes (±)-**5** and (±)-**6**, experimental procedures and data for (*S*)-triflate **9** and (*S*)-monol **10**, and chiral HPLC traces for (±)-**4**, (*S*)-**4**, and (*R*)-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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