

Supplementary Information for:

Synthesis of a [2.2]Paracyclophane Based Planar Chiral Palladacycle by a Highly Selective Kinetic Resolution/C-H Activation Reaction

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General Experimental Methods:

All reactions were routinely performed under air using anhydrous solvents. Anhydrous THF and hexane were obtained by distillation from Na/benzophenone. Anhydrous CH₂Cl₂ was distilled over P₂O₅. Anhydrous toluene was obtained by distillation from sodium metal. All reagents and chemicals were obtained commercially and used as received. Petroleum ether refers to 40-60 petroleum ether. Flash chromatography was carried out using silica gel (0.040-0.063 mm) and eluents as indicated. TLC was carried out on Merck aluminium-backed silica gel sheets and visualised with a UV lamp or by staining with KMnO₄. ¹³C spectra are proton-decoupled. Structural assignments are supported by ¹³C-DEPT and 2D-COSY, HMQC and HMBC spectra. NMR spectra were recorded at room temperature on a Varian 400 Lambda spectrometer operating at 400 MHz for ¹H NMR, 101 MHz for ¹³C NMR. Solvent peaks are used as internal reference relative to Me₄Si for ¹H NMR and ¹³C NMR chemical shifts (ppm). Coupling constants are given in Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra were recorded on a Perkin-Elmer 1720X FT-IR spectrophotometer. Optical Rotations were recorded on a Bellingham & Stanley ADP 440 Polarimeter. Melting points are uncorrected and were recorded using a Büchi Melting Point B-545 apparatus. The pH was measured with a Hanna PH 20 Desktop pH Meter. HPLC separations were performed with a VWR Hitachi Elite LaChrom L-2000 series HPLC system fitted with either a Eurocel 01-5µm chiral column or a Chiralcel OD column. Solvents used (hexane and isopropanol) were of HPLC grade.

Synthesis of racemic 4-acetyl[2.2]paracyclophane: ¹

[2.2]Paracyclophane (2.00 g, 9.6 mmol) was added in one portion to a stirred solution of powdered anhydrous aluminium chloride (2.30 g, 17.2 mmol) and acetyl chloride (1.35 mL, 19 mmol) in CH₂Cl₂ (50 mL) at -30 °C. The resulting reaction mixture was stirred for twenty minutes between -15°C and -20°C, after which dilute HCl was added until the white precipitate dissolved. The resulting reaction mixture was then allowed to slowly warm to room temperature, and stirred at room temperature for 17 hours. The aqueous phase was separated and extracted with 2 x 20 mL of CH₂Cl₂. The combined organic layers were successively washed with a saturated aqueous solution of NaHCO₃ (30 mL) and with water (30 mL), were then dried over MgSO₄, filtrated and evaporated *in vacuo* to give white crystals. Purification by flash column chromatography on silica gel (90/10: petroleum ether / EtOAc) gave the title compound (1.58 g, 66% yield) as a white solid. R_f = 0.45 (80/20: petroleum ether / EtOAc). Mp = 102-104°C. ¹H NMR (CDCl₃, 400MHz): δ (ppm) 2.76 (1H, dt, J= 8, 4 Hz), 2.91-2.99

(2H, m), 2.95 (3H, s), 3.05-3.17 (4H, m), 3.84-3.93 (1H, m), 6.31 (1H, dd, $J = 8, 2$ Hz), 6.38-6.50 (4H, m), 6.56 (1H, dd, $J = 8, 2$ Hz), 6.86 (1H, d, $J = 2$ Hz).

Synthesis of racemic [2.2]paracyclophane-4-carboxylic acid (*rac-3*):²

A solution of potassium hydroxide (2.7 g, 48 mmol) in water (15.5 mL) was slowly added to a stirred aqueous solution of bromine (1.1 mL, 21.5 mmol) at 0°C. A solution of racemic 4-acetyl[2.2]paracyclophane (1.65 g, 6.6 mmol) in dioxane (24 mL) was slowly added to the hyperbromite solution with continued cooling and stirring to give a light orange precipitate. The reaction mixture was then stirred for 10 minutes at 0°C, and the solution was allowed to warm to room temperature to give a homogenous mixture. After 3 hours an 8% aqueous solution of NaHSO₃ (50 mL) was introduced to oxidize the excess bromine. The aqueous phase was basified with a saturated aqueous solution of NaHCO₃ (2 mL) and with water (30 mL), and extracted with CH₂Cl₂ (2 x 20 mL). The aqueous phase was then acidified with a 2M aqueous solution of HCl (12 mL) and the product was extracted with CH₂Cl₂ (6 x 20 mL). The combined organic layers were dried over MgSO₄, filtrated and evaporated *in vacuo* to give colourless crystals (1.66g, >99% yield). R_f = 0.20 (95/5: petroleum ether / EtOAc). IR (CH₂Cl₂): ν (cm⁻¹) 438, 1240, 1367, 1684, 2925. ¹H NMR (CDCl₃, 400MHz): δ (ppm) 2.80-2.86 (1H, m), 2.81 (1H, s), 2.97-3.15 (6H, m), 4.12 (1H, ddt, $J = 10, 2, 1$ Hz), 6.45-6.53 (5H, m), 6.74 (1H, dd, $J = 8, 2$ Hz), 7.21 (1H, d, $J = 2$ Hz).

Synthesis of racemic 4-*N,N*-dimethylamido[2.2]paracyclophane(*rac-4*):

Oxalyl chloride (0.381 g, 3 mmol) was slowly added to a solution of racemic [2.2]paracyclophane-4-carboxylic acid (*rac-3*) (0.690 g, 2.73 mmol) in CH₂Cl₂ (13.8 mL) at room temperature. DMF (0.18 mL, 2 mmol) was subsequently added dropwise. The reaction mixture was stirred for 5 hours at room temperature, and a solution of dimethylamine in water (40 wt.% solution in water, 14 mL) was added. The reaction mixture was subsequently stirred vigorously for 16 hours. The organic phase was separated, successively washed with a saturated aqueous solution of NaHCO₃ (5 mL) and with water (5 mL), dried over MgSO₄, filtrated and evaporated *in vacuo* to give a white powder. Purification by flash column chromatography on silica gel (80/20: petroleum ether / EtOAc) gave the title compound **4** (0.570 g, 75% yield). R_f = 0.34 (95/5: CH₂Cl₂ / Methanol). Mp: 202-206°C. IR (CH₂Cl₂): ν (cm⁻¹) 735, 1265, 1634, 3011. ¹H NMR (CDCl₃, 400MHz): δ (ppm) 2.59 (3H, s), 2.87-2.94 (4H, m), 3.02 (3H, s), 3.05-3.20 (4H, m), 6.33 (1H, t, $J = 2$ Hz), 6.35 (1H, t, $J = 2$ Hz), 6.41-6.52 (4H, m), 7.01 (1H, dd, $J = 8, 2$ Hz). ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 33.55 (CH₂), 34.95 (CH₃), 35.14 (CH₂), 35.22 (CH₂), 35.32 (CH₂), 38.39 (CH₃), 130.79 (Ar, CH), 131.70 (Ar, CH), 132.32 (Ar, CH), 132.62 (Ar, CH), 132.98 (Ar, CH), 133.09 (Ar, C_{quaternary}), 134.20 (Ar, CH), 134.87 (Ar, CH), 137.70 (Ar, C_{quaternary}),

139.11 (Ar, C_{quaternary}), 139.33 (Ar, C_{quaternary}), 139.78 (Ar, C_{quaternary}), 171.13 (Amide, CO, C_{quaternary}).
High-resolution MS (*m/z*, ES): Calcd for C₁₉H₂₂NO: 280.1696. Found: 280.1701.

Synthesis of racemic 4-*N,N*-dimethylamino[2.2]paracyclophane (*rac-5*):

To a solution of lithium aluminium hydride (0.220 g, 5.8 mmol) in anhydrous THF (20 mL) at room temperature, a solution of the racemic 4-*N,N*-dimethylamido[2.2]paracyclophane (*rac-4*) (0.235 g, 0.84 mmol) in anhydrous THF (5 mL) was added dropwise. After the addition was complete, the solution was stirred for 17 hours. The reaction was quenched with a 2M aqueous solution of HCl (15 mL) at 0°C. The aqueous layer was separated, extracted with CH₂Cl₂ (3 x 10 mL), basified with a 3M aqueous solution of NaOH (15 mL), and finally extracted with CH₂Cl₂ (5 x 10 mL). The combined organic layers were dried over MgSO₄, filtrated and evaporated *in vacuo* to give the title compound **4**, as a white powder (0.178 g, 80% yield). Mp: 42-46°C. IR (CH₂Cl₂): ν (cm⁻¹) 717, 1653, 2095, 3430. ¹H NMR (CDCl₃, 400MHz): δ (ppm) 2.08 (6H, s), 2.72-2.80 (1H, m), 2.86-3.08 (7H, m), 3.43-3.67 (2H, m), 6.19 (1H, s), 6.30-6.46 (5H, m), 6.53 (1H, d, *J* = 8 Hz). ¹³C NMR (CDCl₃, 101MHz): δ (ppm) 33.32 (CH₂), 34.42 (CH₂), 34.89 (CH₂), 35.26 (CH₂), 45.40 (CH₃), 62.82 (CH₂), 128.90 (Ar, CH), 131.63 (Ar, CH), 132.05 (Ar, CH), 133.14 (Ar, CH), 133.28 (Ar, CH), 134.82 (Ar, CH), 135.45 (Ar, CH), 137.02 (Ar, broad singlet, C_{quaternary}), 138.75 (Ar, C_{quaternary}), 139.35 (Ar, C_{quaternary}), 139.51 (Ar, C_{quaternary}), 139.52 (Ar, C_{quaternary}). High-resolution MS (*m/z*, ES): Calcd for C₁₉H₂₄N: 266.1903. Found: 266.1906.

Racemic synthesis of monomeric hexafluoroacetylacetonate palladium (II) complex (*rac-7*) from racemic 4-*N,N*-dimethylamino[2.2]paracyclophane (*rac-5*) – Procedure 1:

A suspension of racemic 4-*N,N*-dimethylamino[2.2]paracyclophane (*rac-5*) (0.050 g, 0.19 mmol) and Pd(OAc)₂ (0.042 g, 0.19 mmol) in anhydrous toluene (11 mL) was heated at 60°C for 19 h. The reaction mixture was evaporated *in vacuo* to give complex **6** as a brown solid. This residue was used without further purifications in the following step. Data for **6**: ¹H NMR (CDCl₃, 400MHz): δ (ppm) 2.02 (3H, s), 2.57 (3H, s), 2.60 (3H, s), 2.78-3.16 (7H, m), 3.20 (1H, d, *J* = 16 Hz), 3.28 (1H, d, *J* = 16 Hz), 3.42 (1H, d, *J* = 16 Hz), 5.59-6.18 (2H, m), 6.31-6.45 (2H, m), 6.59 (1H, d, *J* = 10 Hz), 6.77 (1H, d, *J* = 10 Hz). Complex **6** was dissolved in a solution of acetone (3.5 mL) and water (1.5 mL), and sodium hexafluoroacetylacetonate (0.072 g, 0.31 mmol) was added. After stirring at room temperature for 18.5 h, the aqueous layer was separated and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried over MgSO₄, filtrated and evaporated *in vacuo* to give a brown solid. Purification by flash column chromatography on silica gel (80/19/1: petroleum ether / EtOAc / Et₃N, then 98/2: CH₂Cl₂ / MeOH) gave complex **7** (0.012 g, 25% yield), as a yellow glass solid. Mp: 54-58°C. IR (CH₂Cl₂): ν (cm⁻¹) 796, 1150, 1258, 1639, 2855, 2925. ¹H NMR (CDCl₃, 400MHz): δ (ppm) 2.51 (3H,

s), 2.60-2.75 (2H, m), 2.78 (3H, s), 2.78-3.02 (5H, m), 3.60 (1H, d, $J = 14$ Hz), 3.69 (1H, t, $J = 12$ Hz), 4.08 (1H, d, $J = 14$ Hz), 6.03-6.09 (3H, m), 6.40 (1H, d, $J = 8$ Hz), 6.56 (1H, d, $J = 8$ Hz), 6.73 (1H, d, $J = 8$ Hz), 6.83 (1H, d, $J = 8$ Hz). ^{13}C NMR (CDCl_3 , 101MHz): δ (ppm) 33.82 (CH_2), 34.48 (CH_2), 34.80 (CH_2), 35.50 (CH_2), 52.56 (CH_3), 72.29 (CH_2), 90.57 (FACAc, CH), 117.67 (FACAc, q, $J_F = 285.6$ Hz, CF_3 , $\text{C}_{\text{quaternary}}$), 126.26 (Ar, CH), 130.95 (Ar, CH), 131.81 (Ar, CH), 132.30 (Ar, CH), 132.69 (Ar, $\text{C}_{\text{quaternary}}$), 133.10 (Ar, CH), 133.55 (Ar, CH), 138.03 (Ar, $\text{C}_{\text{quaternary}}$), 140.93 (Ar, $\text{C}_{\text{quaternary}}$), 143.02 (Ar, C-Pd, $\text{C}_{\text{quaternary}}$), 144.77 (Ar, $\text{C}_{\text{quaternary}}$), 144.85 (Ar, $\text{C}_{\text{quaternary}}$), 174.53 (FACAc, q, $J_F = 34.4$ Hz, CO, $\text{C}_{\text{quaternary}}$), 175.17 (FACAc, q, $J_F = 34.5$ Hz, CO, $\text{C}_{\text{quaternary}}$). High-resolution MS (m/z , p-APCI): Calcd for $\text{C}_{24}\text{H}_{24}\text{F}_6\text{NO}_2\text{Pd}$: 578.0741. Found: 578.0758. This complex was subjected to hplc analysis to give **trace 0 (racemate)** (Cf. hplc **trace 0 (racemate)** in **annexe II**).

Small scale kinetic resolution of racemic 4-*N,N*-dimethylamino[2.2]paracyclophane (*rac-5*)

Typical Procedure – Procedure 2:

Table 1, entry 1

N-Acetyl-D-phenylalanine³ (0.039 g, 0.19 mmol) was dissolved in a 0.3M solution of NaOH in water (630 μL , 0.19 mmol). The resulting solution was added to a solution of Na_2PdCl_4 (0.0277 g, 0.094 mmol) in MeOH (2.4 mL), and the pH of the resulting solution was adjusted to 8.2 with a 50% aqueous solution of NaOH. To this solution was added a solution of racemic 4-*N,N*-dimethylamino[2.2]paracyclophane (*rac-5*) (0.050 g, 0.19 mmol) in a 4/1 mixture of MeOH and CH_2Cl_2 (4.3 mL). The reaction mixture was subsequently stirred for 18 hours at room temperature, the organic solvents were removed *in vacuo* and the residue was dissolved in a 2/1 mixture of acetone and water (9.4 mL). Sodium hexafluoroacetylacetonate (0.108 g, 0.47 mmol) was added, and after stirring at room temperature for 18 hours, the organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were dried over MgSO_4 , filtrated and evaporated *in vacuo* to give a brown solid. Purification by flash column chromatography on silica gel (80/19/1: petroleum ether / EtOAc / Et_3N , then 98/2: CH_2Cl_2 / MeOH) gave complex **7** (0.018 g, 33% yield) as a yellow glass solid. This complex was subjected to hplc analysis to give **trace 1** (Cf. hplc **trace 1** in **annexe II**, ee = 97.8%). Furthermore, the unreacted starting 4-*N,N*-dimethylamino[2.2]paracyclophane **5** (0.028 g, 56% yield) was also recovered after column chromatography, and was converted into complex **7** (0.021 g, 0.036 mmol) following **procedure 1** in 34% yield. This complex was also subjected to hplc analysis giving **trace 1'** (Cf. hplc **trace 1'** in **annexe II**, ee = 75.2%). **Procedure 2 was used for all the small scale reactions reported in Table 1.**

Measured $[\alpha]_{\text{D}}$ for compound (*S_p*)-5 (ee = 97.5%) – Table 1, entry 4: $[\alpha]_{\text{D}}^{29.5^\circ\text{C}}$ (c = 0.95 g/dL, CHCl_3) = +61.1.

Measured $[\alpha]_D$ for compound (*S_p*)-**7** (ee = 97.8%) – Table 1, entry 1: $\alpha_D^{28.4^\circ\text{C}}$ (c = 0.85 g/dL, CHCl₃) = +151.5.

Large scale kinetic resolution of racemic 4-*N,N*-dimethylamino[2.2]paracyclophane (*rac*-**5**)

Typical Procedure – Procedure 3:

Table 1, entry 5

A solution of *N*-Acetyl-D-phenylalanine (0.729 g, 3.52 mmol) and NaOH (0.141 g, 3.52 mmol) in water (11.2 mL) was added to a solution of Na₂PdCl₄ (0.518 g, 1.76 mmol) in MeOH (44 mL), and the pH of the resulting solution was adjusted to 8.2 with a 50% aqueous solution of NaOH. To this solution, a solution of racemic 4-*N,N*-dimethylamino[2.2]paracyclophane (*rac*-**5**) (0.934 g, 3.52 mmol) in 4:1 MeOH/CH₂Cl₂ (80 mL) was added. The reaction mixture was subsequently stirred for 17.5 hours at room temperature. The organic layer was collected and the aqueous layer was extracted with CH₂Cl₂ (5 x 10 mL). The combined organic layers were dried over MgSO₄, filtrated and evaporated *in vacuo*. Column chromatography (SiO₂) (80/19/1: petroleum ether / EtOAc / Et₃N, to elute the unreacted amine, then 98/2: CH₂Cl₂ / MeOH) gave crude complex **8**, a brown solid, as a mixture of *cis* and *trans* isomers (0.367 g). Data for the crude complex **8**: ¹H NMR (CDCl₃, 400MHz): δ (ppm) 2.88-3.15 (16H, m), 3.08 (3H, s, Me), 3.09 (3H,s, Me), 4.04 (2H, d, *J* = 17.0 Hz), 4.15 (2H, d, *J* = 17.1 Hz), 6.35-6.52 (10H, m), 6.52 (1H, d, *J* = 7.8 Hz), 6.59 (1H, d, *J* = 7.8 Hz). The dry powder was dissolved in 2:1 acetone/water (21 mL) containing sodium hexafluoroacetylacetonate (0.295 g, 1.28 mmol). After stirring at room temperature for 8 hours, the aqueous layer was separated and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried over MgSO₄, filtrated and evaporated *in vacuo* to give a brown solid. Purification by flash column chromatography on silica gel (98/2: CH₂Cl₂ / MeOH) gave complex **7** (0.356 g, 35 % yield), as a yellow glass solid. This complex was subjected to hplc analysis to give **trace 5** (*Cf.* hplc **trace 5** in **annexe II**, ee = 99.7%).

Determination of the configuration of the unreacted starting 4-*N,N*-dimethylamino[2.2]paracyclophane **5**. Synthesis of 4-formyl[2.2]paracyclophane **9** from 4-*N,N*-dimethylamino[2.2]paracyclophane **5**.

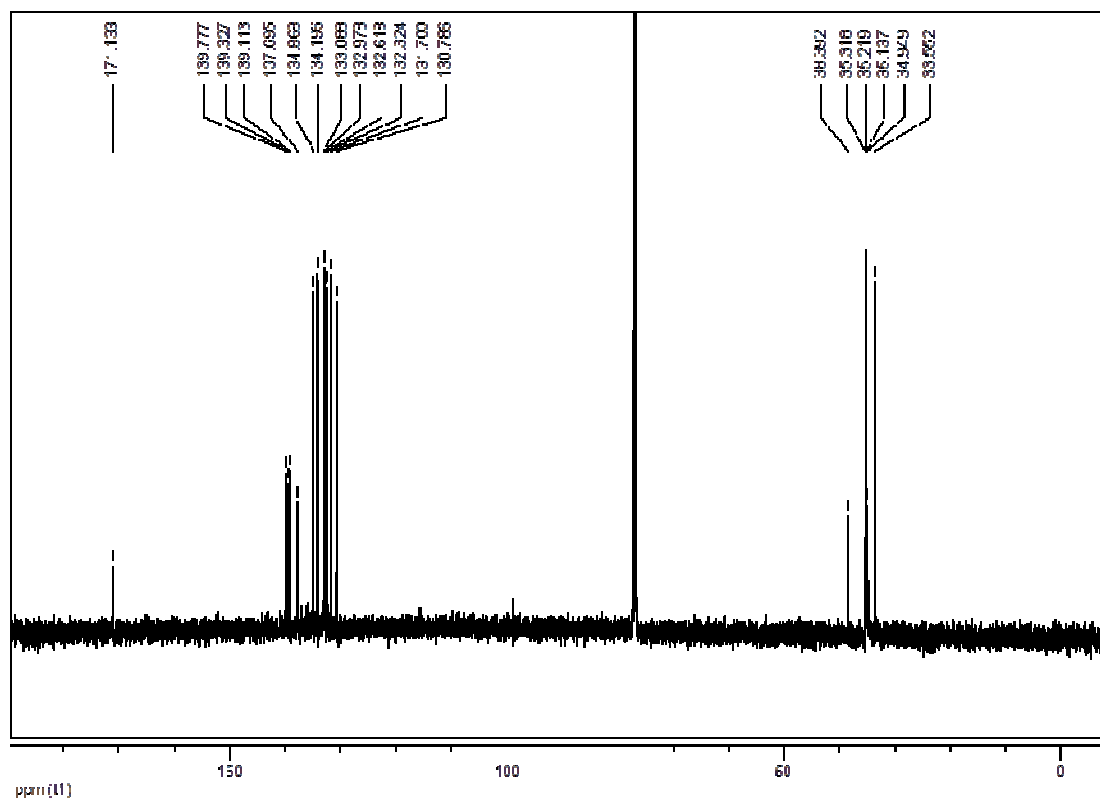
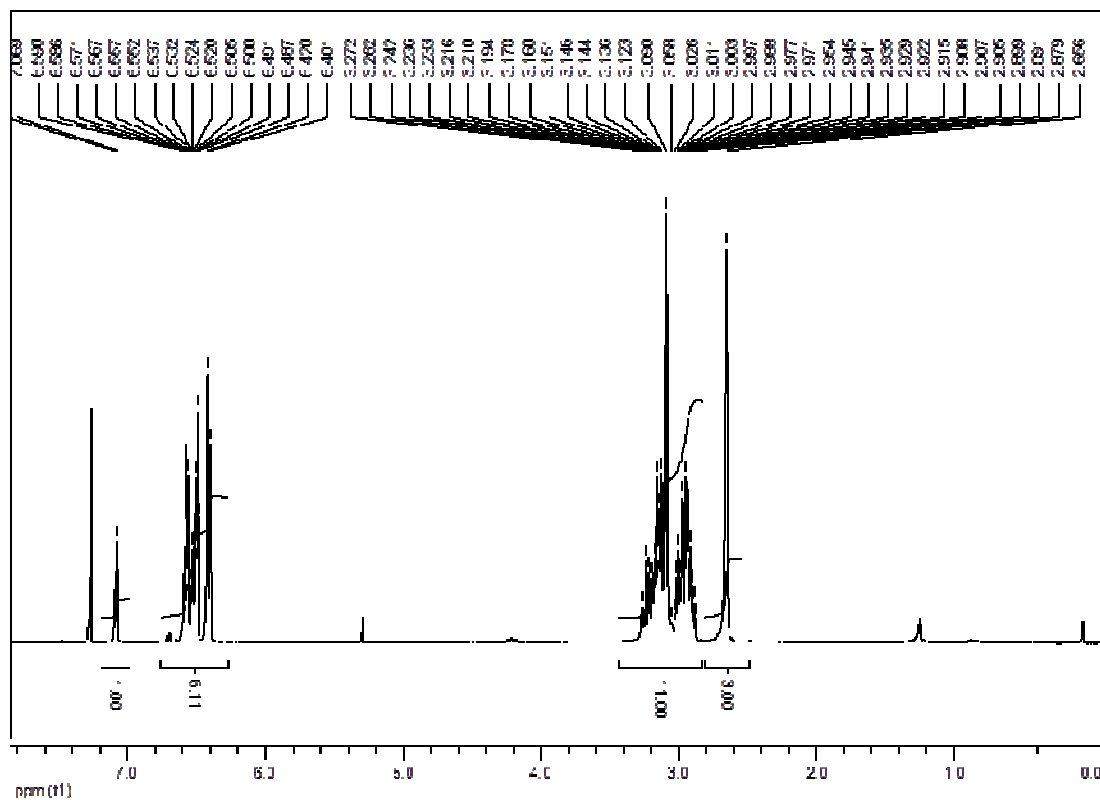
The unreacted starting 4-*N,N*-dimethylamino[2.2]paracyclophane **5** (ee = 97.5%), recovered from the kinetic resolution described in **Table 1, entry 4**, was isolated and converted into the corresponding enantioenriched 4-formyl[2.2]paracyclophane **9** in one step, following a known synthetic procedure from the literature.⁴ The specific rotation of the enantioenriched 4-formyl[2.2]paracyclophane **9** thus

obtained, was subsequently compared with the data already reported in the literature for this compound.⁵

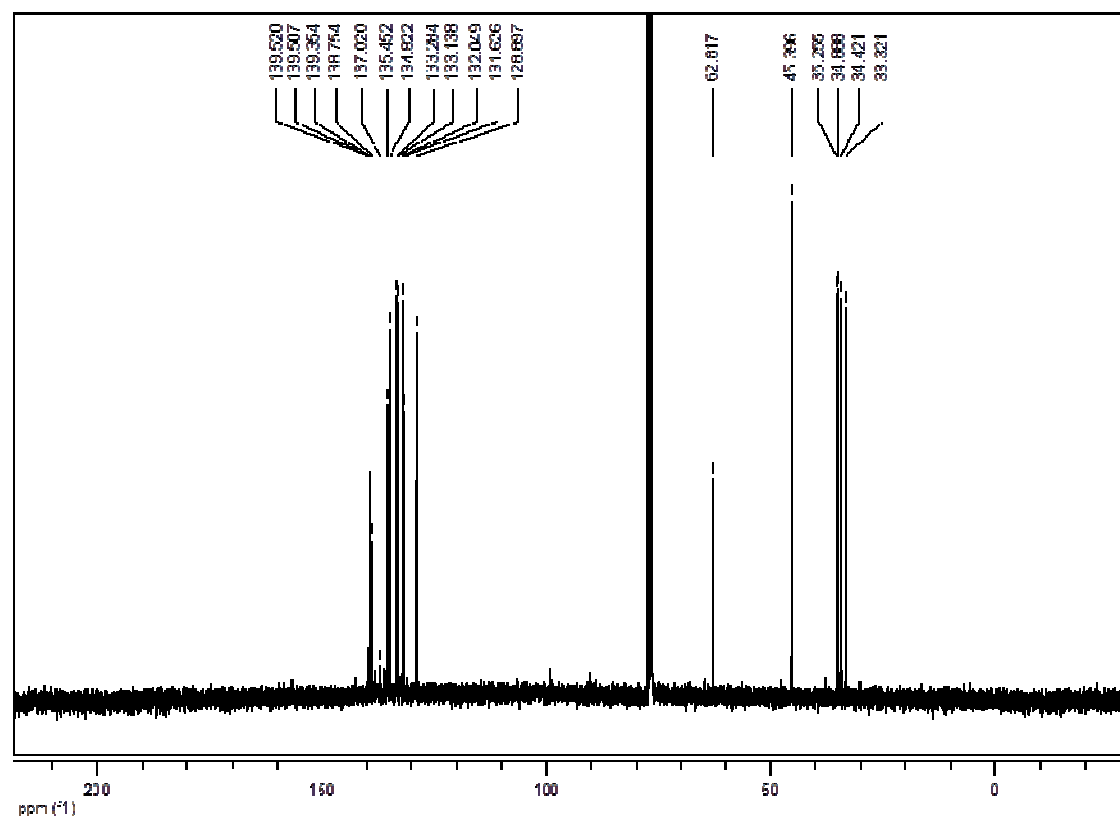
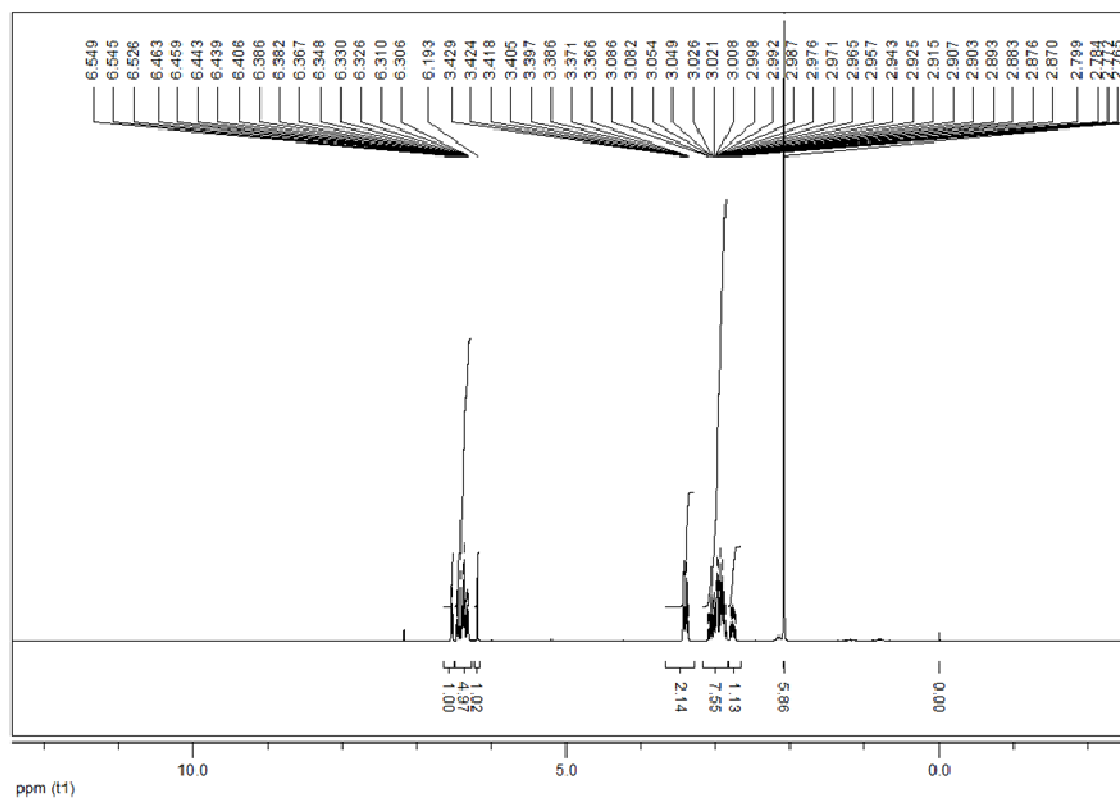
To a stirred solution of 4-*N,N*-dimethylamino[2.2]paracyclophane **5** (ee = 97.5%) (0.030 g, 0.11 mmol) in 0.6 mL of reagent grade benzene was added *N*-bromosuccinimide (0.0201 g, 0.11 mmol, freshly recrystallized from water and dried over P₂O₅) at 25°C. The stoppered reaction mixture was stirred at 25°C for 20 h, and then 1 mL of water was added. The resulting mixture was stirred vigorously under air for 3 h and the organic layer was separated, washed with a brine-NaHCO₃ mixture, dried (Na₂SO₄), and evaporated *in vacuo*. The oily residue was chromatographed on a column of silica gel using 1:1 CH₂Cl₂/hexane, as eluent. Evaporation of the volatiles gave 0.014 g (56%) of the aldehyde as a white solid. The ¹H and ¹³C NMR spectra for this aldehyde compared with those already reported in the literature for this compound.⁶ ¹H NMR (CDCl₃, 400MHz): δ (ppm) 2.91-3.30 (7, m), 4.10 (1H, ddd, *J*= 12, 10, 2 Hz), 6.37 (1H, dd, *J*= 8, 2 Hz), 6.43 (1H, dd, *J*= 8, 2 Hz), 6.50 (1H, dd, *J*= 8, 2 Hz), 6.56 (1H, dd, *J*= 8, 2 Hz), 6.59 (1H, d, *J*= 8 Hz), 6.73 (1H, dd, *J*= 8, 2 Hz), 7.02 (1H, d, *J*= 2 Hz), 9.95 (1H, s). ¹³C NMR (CDCl₃, 100MHz): δ (ppm) 33.6 (CH₂), 35.0 (CH₂), 35.1 (CH₂), 35.2 (CH₂), 132.1 (Ar, CH), 132.4 (Ar, CH), 132.9 (Ar, CH), 133.2 (Ar, CH), 136.1 (Ar, CH), 136.3 (Ar, CH), 136.5 (Ar, C_{quaternary}), 138.1 (Ar, CH), 139.4 (Ar, C_{quaternary}), 139.5 (Ar, C_{quaternary}), 140.6 (Ar, C_{quaternary}), 143.2 (Ar, C_{quaternary}), 191.9 (Aldehyde, CO, C_{quaternary}). High-resolution MS (*m/z*, p-APCI): Calcd for C₁₇H₁₇O (M+H)⁺: 237.1274. Found: 237.1269. Measured [α]_D^{23.9°C} = +178.7 (c = 0.6, CHCl₃), which corresponds to the (*S*) enantiomer. {Literature data for the (*S*) enantiomer (98.7% (HPLC))⁵: [α]_D^{25°C} = +184 (c = 0.41, CHCl₃)}.}

Annexe I: ^1H and ^{13}C NMR Spectra of compounds 4, 5, 7, and 9.

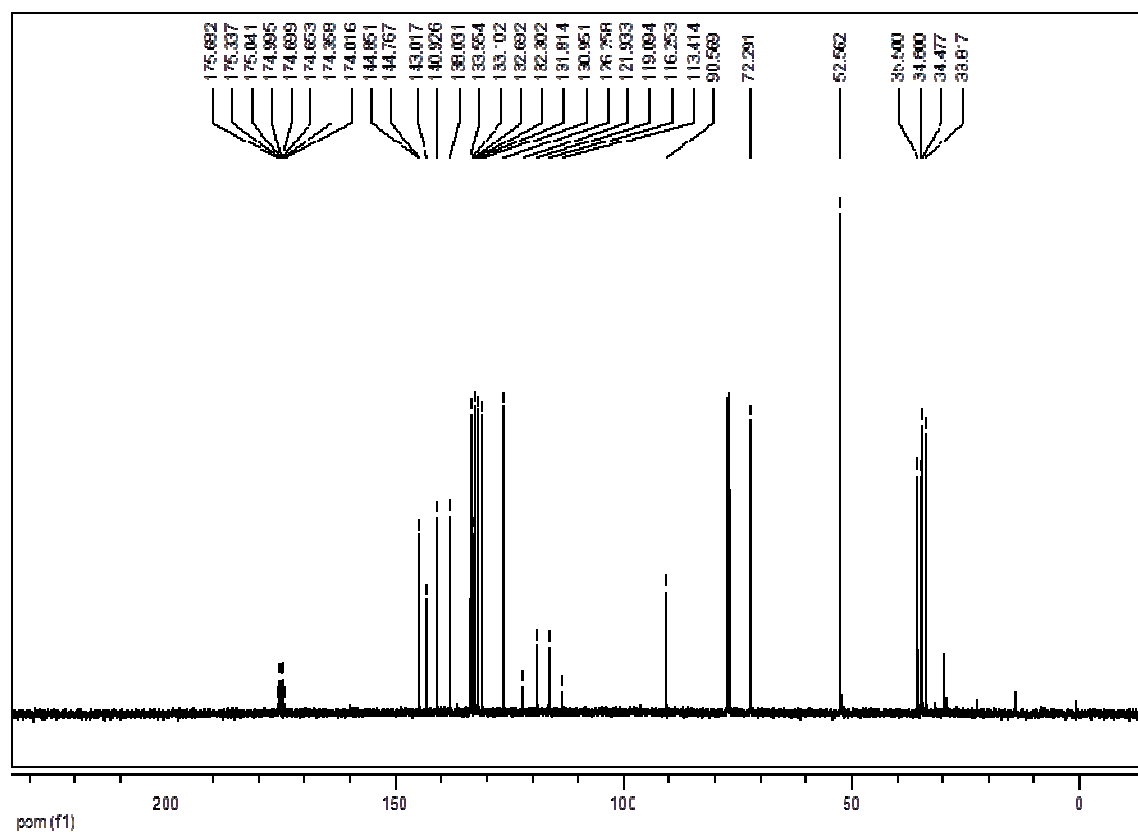
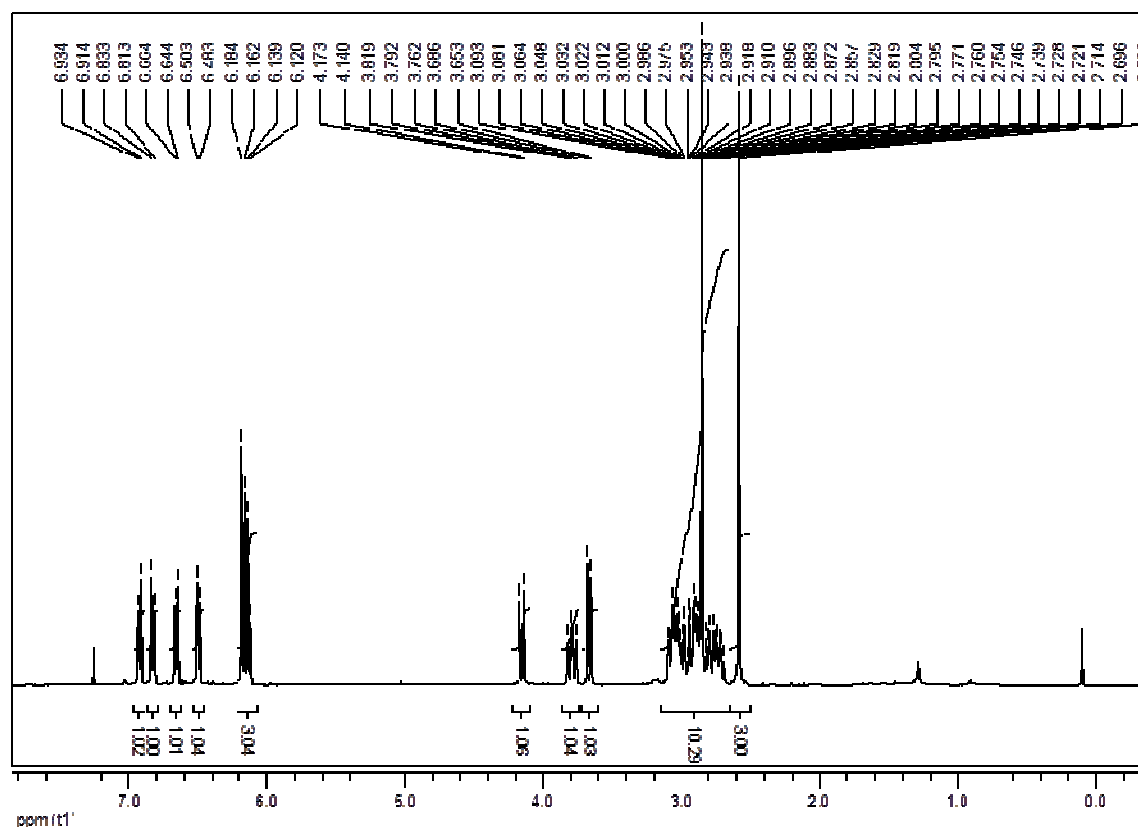
^1H and ^{13}C NMR spectra of (*rac*)-4.



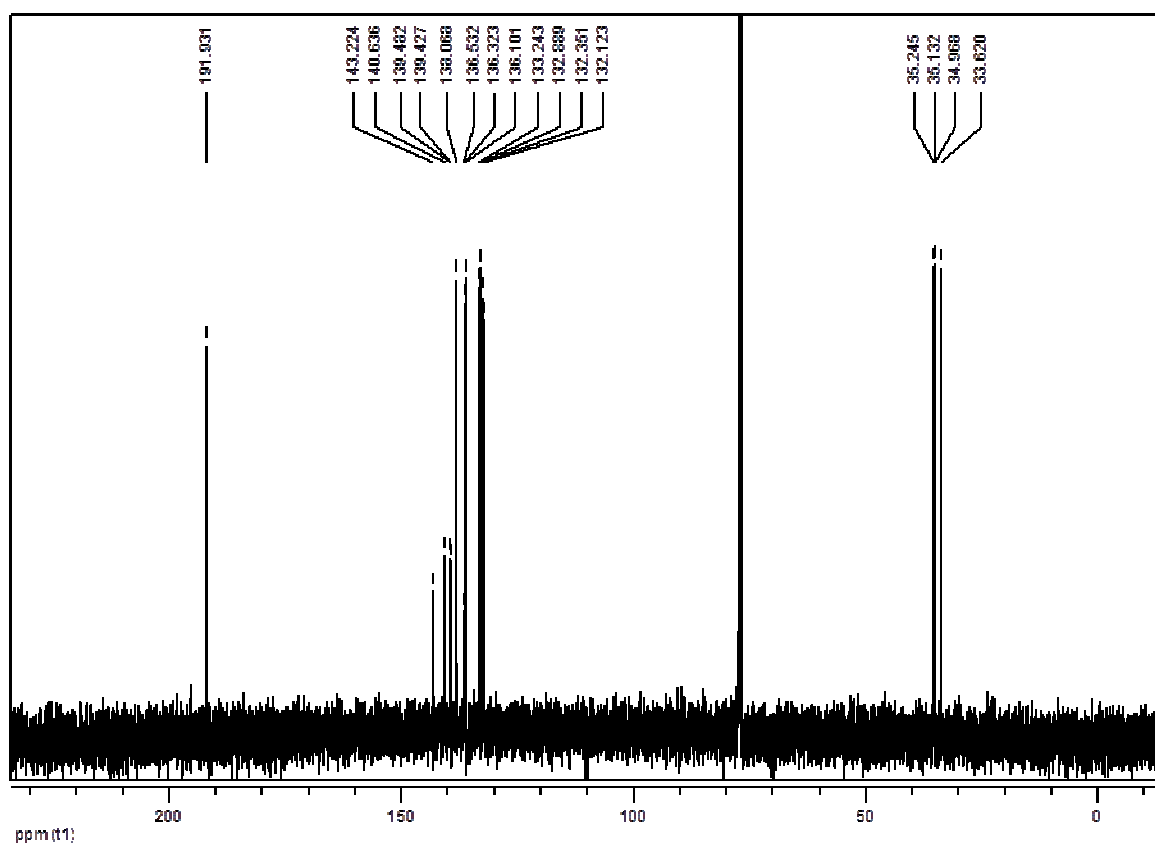
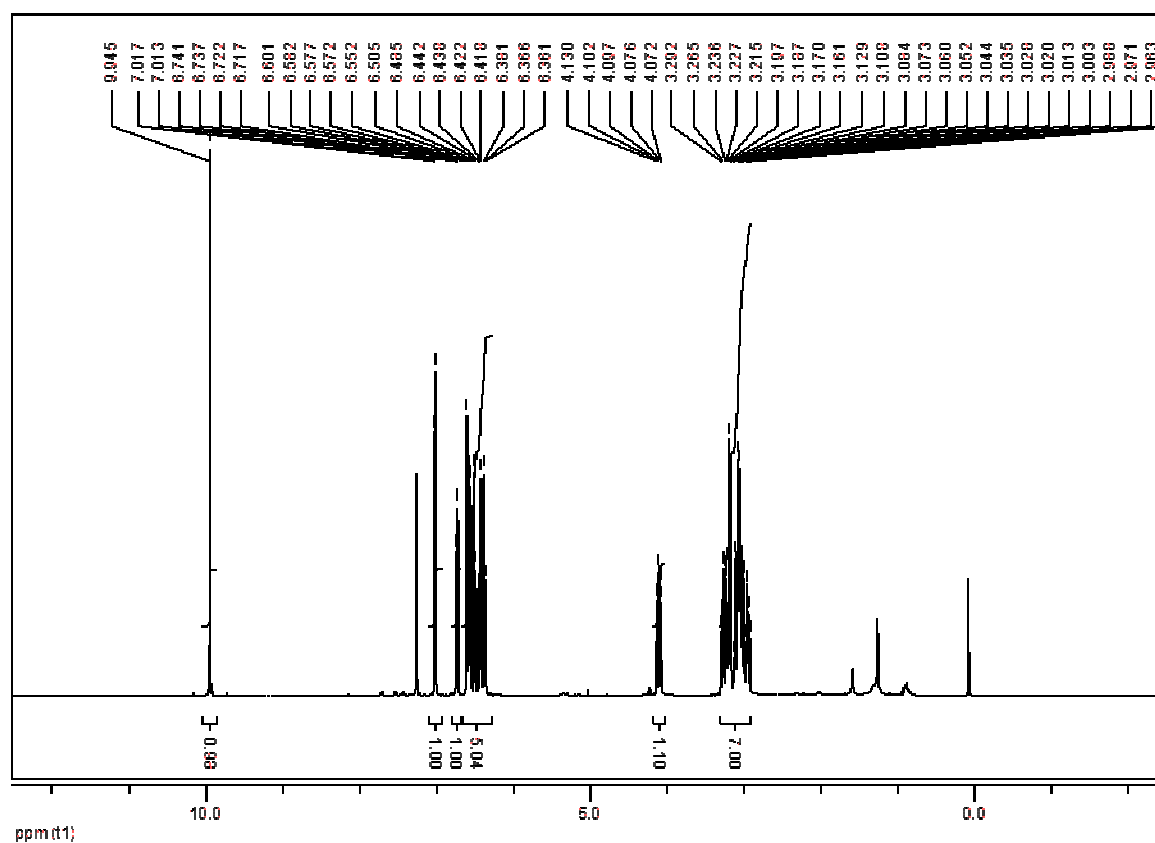
^1H and ^{13}C NMR spectra of (*rac*)-5.



^1H and ^{13}C NMR spectra of **7**.



^1H and ^{13}C NMR spectra of **9**.

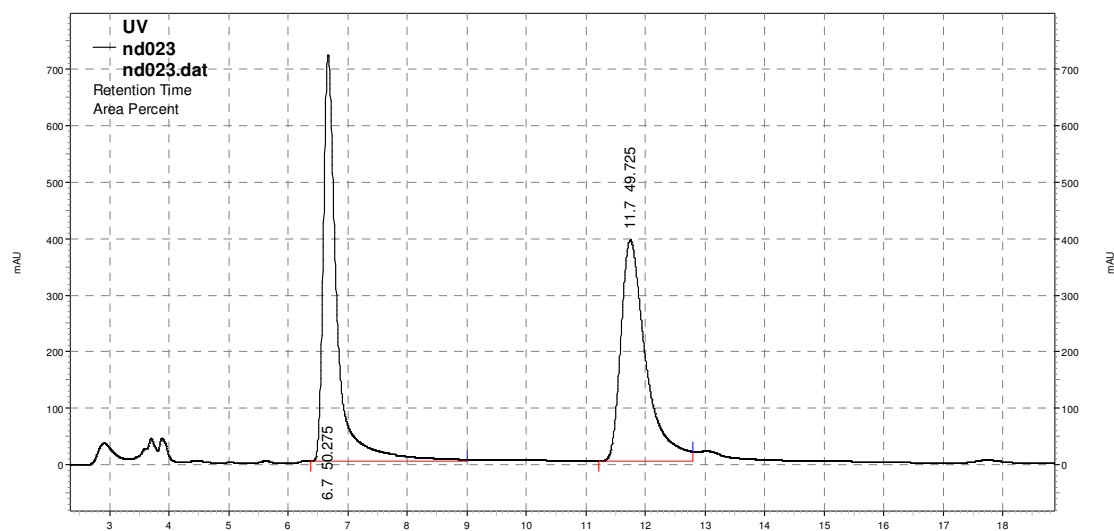


Annexe II: HPLC traces 0 and 1, 1', 5.

5% IPA/95% Hexane, 1mL 30min

i) trace 0 (racemate) [Eurocel 01-5 μ m chiral column]

Area % Report



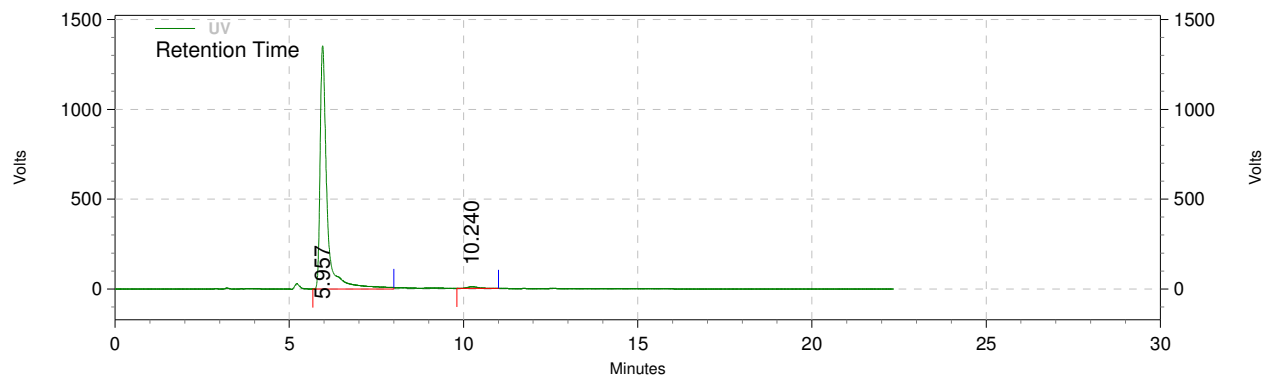
UV Results

Retention Time	Area	Area %	Height	Height %
6.670	45896374	50.27	2873500	64.79
11.743	45394358	49.73	1561334	35.21

Totals	Area	Area %	Height	Height %
	91290732	100.00	4434834	100.00

ii) trace 1 (97.8% ee sample) - Table 1, entry 1 [Eurocel 01-5 μ m chiral column]

Area % Report



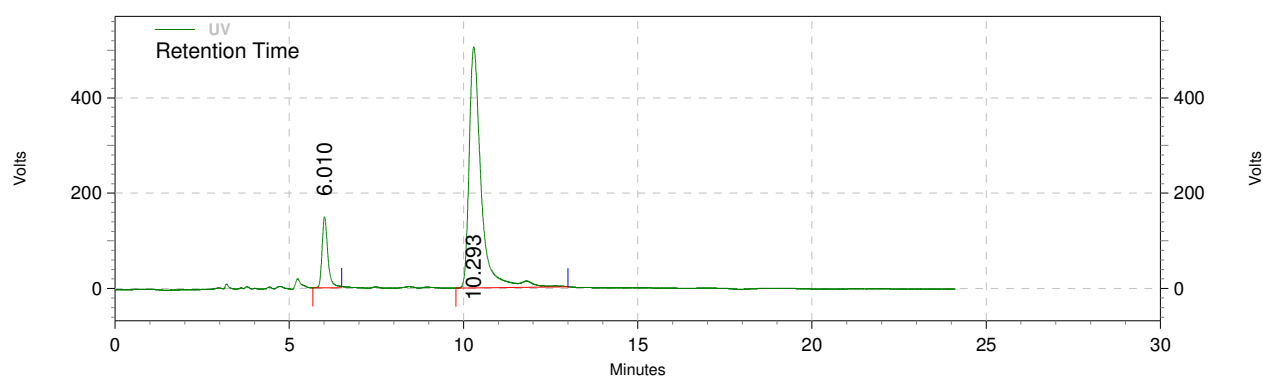
UV Results

Retention Time	Area	Area %	Height	Height %
5.957	74771270	98.90	5418640	99.29
10.240	833209	1.10	38601	0.71

Totals	75604479	100.00	5457241	100.00
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iii) trace 1' (75.2% ee sample) - Table 1, entry 1 [Eurocel 01-5 μ m chiral column]

Area % Report



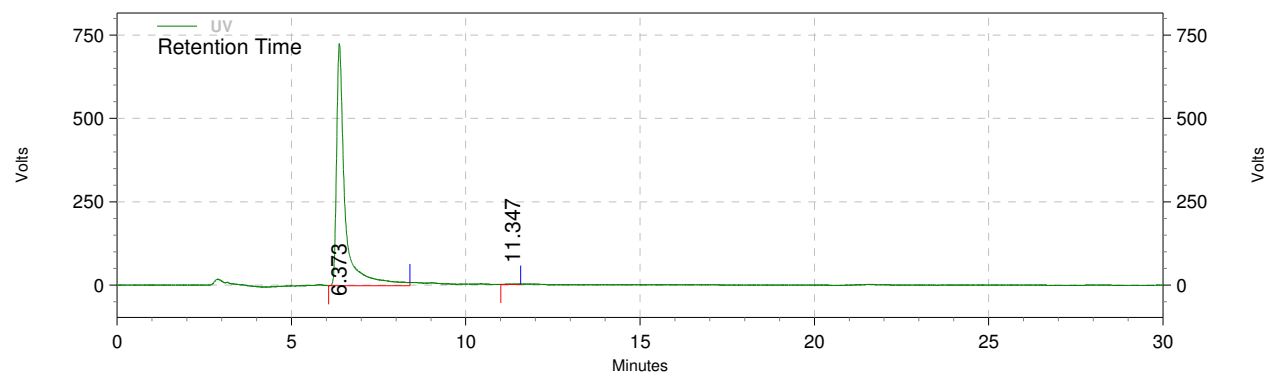
UV Results

Retention Time	Area	Area %	Height	Height %
6.010	6836635	12.40	596114	22.75
10.293	48305674	87.60	2024276	77.25

Totals	55142309	100.00	2620390	100.00
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iv) trace 5 (>99% ee sample) - Table 1, entry 5 [Chiralcel OD column]

Area % Report



UV Results

Retention Time	Area	Area %	Height	Height %
6.373	48781023	99.86	2904974	99.88
11.347	69212	0.14	3367	0.12

Totals	48850235	100.00	2908341	100.00
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References

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