Synthesis of All Possible Stereoisomers of α-Branched [2.2]Paracyclophanylalkylamines

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Abstract: The synthesis of all four possible stereoisomers of enantiopure and diastereomerically pure or highly enriched α-branched [2.2]paracyclophanylalkylamines is described. Key step is the nucleophilic 1,2-addition of alkylithium reagents to hydrazones of 4-formyl[2.2]paracyclophane derived from the chiral auxiliaries SAMP/RAMP and RAMBO/SAMBO via chromatographic epimer separation. Reductive N–N bond cleavage of the resulting hydrazines, followed by treatment with benzyloxy carbonyl chloride afforded the N-Cbz-protected diastereo- and enantiopure (de, ee ≥ 99%) or diastereomerically enriched (de = 89–96%) title amines.

Key words: amines, cyclophanes, hydrazones, nucleophilic addition, planar chirality

During the last ten years, a focus in paracyclophane chemistry has been the development and design of substituted chiral [2.2]paracyclophanes as ligands in asymmetric catalysis.1 Many applications were reported and probably the most prominent example is Phanephos, a planar chiral C2-symmetrical bisphosphine ligand.2 Other goals of current syntheses of substituted [2.2]paracyclophanes are molecules bearing a nitrogen containing substituent in the 4-position,3 such as the amino function. The asymmetric synthesis of amines by nucleophilic 1,2-addition of organometallic reagents to the C=N bond is well developed and described.4 The addition of nucleophilic reagents to the C=N bond of hydrazones leads to hydrazines, whose N–N bond can be cleaved under reductive conditions to obtain amines. Especially the SAMP/RAMP-hydrazone methodology has proven to provide an efficient entry to enantioselectively pure amines.5 Related chiral hydrazones based on the proline structure have also been successfully utilized in the same reaction.4a,6 In view of further applications of α-branched [2.2]paracyclophanylalkylamines as ligands in asymmetric catalysis, and regarding the tuning and optimized performance of such catalysts, the access to all possible stereoisomers is highly desirable.

In a preceding communication, we described a flexible synthesis of Rp,R- and Sp,S-configured α-branched [2.2]paracyclophanylalkylamines by addition of alkyllithium reagents to enantiomerically pure 4-formyl[2.2]paracyclophane N,N-dimethylhydrazones as the key step (Scheme 1).7 We now wish to report in detail on the synthesis of all possible stereoisomers of α-branched [2.2]paracyclophanylalkylamines, especially those with Rp,S- and Sp,R-configuration and the corresponding formerly inaccessible methylamines.7

Scheme 1 Synthesis of N-protected α-branched [2.2]paracyclophanylalkylamines7

As shown in Scheme 2, the diastereoselective synthesis of α-branched [2.2]paracyclophanylalkylamines starts from 4-formyl[2.2]paracyclophane (rac-1).8 Condensation of this aldehyde with SAMP in chloroform afforded the SAMP-hydrazone 2 in 89% yield. The resulting epimeric mixture was separated by CSP-HPLC (Chiralpak AD) to

Scheme 2 Synthesis and chromatographic epimer separation of 4-formyl[2.2]paracyclophane SAMP-hydrazone 2

R = Et, n-Pr, n-Bu, t-Bu, n-Hex
give the pure planar and central chiral SAMP-hydrazones (Rp, S)-2 and (Sp, S)-2, respectively.

The nucleophilic 1,2-addition of alkylithium reagents to the [2.2]paracyclophanyl hydrazones was carried out in absolute THF at –100 °C. Aqueous workup afforded the hydrazines 3 or 7 (from 6, see below), which were immediately subjected to N–N bond cleavage without further purification. An excess of BH₃·THF (10 equiv) in refluxing THF was used for the reductive N–N bond cleavage. The resulting amines 4 were directly protected with Cbz-Cl as N-carbamates 5. The diastereomeric excesses of the planar and central chiral protected amines were determined by 13C NMR spectroscopy and CSP-HPLC (Schemes 3, 4, Tables 1–3).

Interestingly, a matched/mismatched case was observed. While the (Rₛ,R)-SAMP-hydrazone 2 led to the amines (Rₛ,R)-5a,b,d–f with virtually complete diastereoselectivities (de ≥ 99%, Table 1) including the formerly inaccessible Rₛ,R- and Sₛ,S-configured methylamines 5a (Scheme 4, Table 1), the amines 5a,b,d–f derived from the epimeric (Sₛ,S)-hydrazone 2 were obtained only in low to moderate diastereoselectivity with a de of 13–68% (Scheme 3, Table 2). In the matched case we assume a cooperative effect of the sterically demanding [2.2]paracyclophane moiety and the precomplexation of the hydrazone with the excess organolithium reagent resulting in an excellent diastereofacial selectivity of the nucleophilic Re-face attack. In the mismatched case both steric effects are opposite resulting in the relatively low

Scheme 3 Synthesis of N-protected α-branched [2.2]paracyclophanylalkylamines 5. Reagents and conditions: (a) RLi (3 equiv), THF, –100 °C to r.t.; (b) BH₃·THF, THF, reflux, 4 h; (c) Cbz-Cl, K₂CO₃, CH₂Cl₂/H₂O (2:1), reflux, 72 h.

Scheme 4 Synthesis of (Rₛ,R)- and (Sₛ,S)-benzyl [1-[2.2]paracyclophane-4'-yl]alkyl)carbamates 5. Reagents and conditions: (a) RLi (3 equiv), THF, –100 °C to r.t.; (b) BH₃·THF, THF, reflux, 4 h; (c) Cbz-Cl, K₂CO₃, CH₂Cl₂/H₂O (2:1), reflux, 72 h.
Table 1  \( R_{p,R}\)-Configured \( N\)-Cbz-Protected Amines 5a,b,d,f Prepared Starting from \((R_{p,R})\)-Hydrazone 2 (Matched Case)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)a</th>
<th>de (%)b</th>
<th>ee (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>( (R_{p,R}))-5a</td>
<td>Me</td>
<td>93</td>
<td>≥99</td>
</tr>
<tr>
<td>( (S_{p,S}))-5a</td>
<td>Me\textsuperscript{d}</td>
<td>86</td>
<td>≥99</td>
</tr>
<tr>
<td>( (R_{p,R}))-5b</td>
<td>Et</td>
<td>65</td>
<td>≥99</td>
</tr>
<tr>
<td>( (R_{p,R}))-5d</td>
<td>n-Bu</td>
<td>92</td>
<td>≥99</td>
</tr>
<tr>
<td>( (R_{p,R}))-5e</td>
<td>t-Bu</td>
<td>57</td>
<td>≥99</td>
</tr>
<tr>
<td>( (R_{p,R}))-5f</td>
<td>n-Hex</td>
<td>81</td>
<td>≥99</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Yield over three steps after purification by column chromatography.
\textsuperscript{b}Determined by \(^1\)C NMR spectroscopy and CSP-HPLC (Chiralpak IA; AS).
\textsuperscript{c}Determined by CSP-HPLC (Chiralpak AD; IA; Chiralcel OD).
\textsuperscript{d}Prepared from the enantiomeric \((S_{p,R})\)-hydrazone 2 based on RAMP.

Table 2  \( S_{p,R}\)-Configured \( N\)-Cbz-Protected Amines 5a,d,f Prepared Starting from \((S_{p,R})\)-Hydrazone 2 (Mismatched Case)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)a</th>
<th>de (%)b</th>
<th>ee (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>( (S_{p,R}))-5a</td>
<td>Me</td>
<td>83</td>
<td>45</td>
</tr>
<tr>
<td>( (R_{p,R}))-5a</td>
<td>Me\textsuperscript{d}</td>
<td>74</td>
<td>29\textsuperscript{e}</td>
</tr>
<tr>
<td>( (S_{p,R}))-5d</td>
<td>n-Bu</td>
<td>60</td>
<td>68</td>
</tr>
<tr>
<td>( (S_{p,R}))-5e</td>
<td>t-Bu</td>
<td>52</td>
<td>46</td>
</tr>
<tr>
<td>( (S_{p,R}))-5f</td>
<td>n-Hex</td>
<td>27</td>
<td>13</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Yield over three steps after purification by column chromatography.
\textsuperscript{b}Determined by \(^1\)C NMR spectroscopy and CSP-HPLC (Chiralpak IA; AS).
\textsuperscript{c}Determined by CSP-HPLC (Chiralpak AD; IA; Chiralcel OD).
\textsuperscript{d}Prepared from the enantiomeric \((S_{p,R})\)-hydrazone 2 based on RAMP.
\textsuperscript{e}1,2 addition carried out at –78 °C instead of –100 °C.

The absolute configuration of the newly generated stereogenic center was assigned by an X-ray structure analysis on crystals of the amine \((R_{p,R})-5a\) derived from the hydrazone \((R_{p,R})-2\) (Figure 1).

![Scheme 5](image-url) Synthesis 2008, No. 8, 1288–1296 © Thieme Stuttgart - New York
This $R_p$-configuration of the N-protected amine 5a is in agreement with our previous results on nucleophilic 1,2-additions of organolithium, Grignard, and organocerium reagents to aldehyde-SAMP hydrazones.13 Because all $R_p$,$S$-configured amines 5a–f derived from the ($R_p$,R,R)-hydrazone 6 were obtained as oils and a crystallization failed, the relative configuration of the new stereogenic center was determined spectroscopically by NOE measurements on ($R_p$,$S$)-5a. The absolute configuration was deduced by converting the hydrazone ($R_p$,R,R,R)-6 into its known parent aldehyde ($R_p$)-1.14

Assuming that a uniform mechanism operates in the nucleophilic additions, all protected amines 5a–f starting from hydrazone ($R_p$,$R$,$R$,$R$)-6 should have the $S$-configuration at the newly formed stereogenic center. As expected, the protected methylamine 5a starting from the enantiomeric hydrazone ($S_p$,$S$,$S$,$S$)-6 showed identical spectra (NMR, MS, IR), but an opposite optical rotation.

In conclusion, an efficient and flexible synthesis of diastereomerically highly enriched and enantiomerically pure α-branched amines bearing the rigid and sterically demanding planar chiral [2.2]paracyclophane moiety has been developed. By using the corresponding chiral auxiliaries SAMP or RAMP and RAMBO or SAMBO, respectively, all stereoisomers of the title compounds are accessible. Furthermore, for the first time, the hydrazines RAMBO/SAMBO were employed as chiral auxiliaries in nucleophilic 1,2-additions of alkyllithium reagents to the $C=\text{N}$ bond.

All common reagents were purchased from common commercial suppliers and used from freshly opened containers. Solvents for chromatography and for workup were dried and purified by conventional methods prior to use. THF was freshly distilled from Na/Pb and benzophenone under argon. MeLi, n-BuLi, n-HexLi, BH$_3$/THF (1 M solution in THF), and benzyl chlororormate were purchased form Merck, Chemetall, Acros, and Aldrich. EtLi and n-PrLi were prepared by halogen–metal exchange of the corresponding alkyl iodide with n-BuLi.15 Preparative flash column chromatography was carried out with Merck silica gel 60, particle size 0.040–0.063 mm. Optical rotation values were measured using a PerkinElmer P 241 polarimeter; solvents used were of Merck UVASOL quality. IR spectra: PerkinElmer FT/IR 1760 spectrometer. NMR spectra: Varian Mercury 300 and Varian Inova 400 spectrometers, TMS as internal standard. MS: Finnigan SSQ 7000 (EI, 70 eV) spectrometer. Microanalyses were obtained with a Vario EL element analyzer. Merck TLC plates silica gel 60 F254 were used for TLC analyses and the products were visualized by UV detection or phosphomolybdic acid (5 wt% in EtOH). Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. The chiral auxiliaries SAMP [$S$-1-amino-2-(methoxymethyl)pyrroline], RAMP [$S$-1-amino-2-(methoxymethyl)pyrroline], SAMBO [$S$,$S$-2-amino-3-methoxymethyl-2-azabicyclo[3.3.0]octane], and RAMBO [$S$,$S$,$S$-2-amino-3-methoxymethyl-2-azabicyclo[3.3.0]octane] were prepared from ($S$)-proline, ($R$)-proline, (all-$S$)-2-azabicyclo[3.3.0]octane-3-carboxylic acid benzyl ester hydrochloride and (all-$R$)-2-azabicyclo[3.3.0]octane-3-carboxylic acid benzyl ester hydrochloride employing literature procedures.16

4-Formyl[2.2]paracyclophane SAMP-Hydrazones 2; General Procedure (GP1)

To a solution of racemic 4-formyl[2.2]paracyclophane in CHCl$_3$ (5.1–5.9 mL/mmoll) was added the SAMP and the mixture stirred under reflux until the reaction was complete (8–72 h). The organic phase was dried (MgSO$_4$), and after concentration in vacuo, the hydrazide was purified by flash column chromatography (SiO$_2$, n-pentane–Et$_2$O, 4:1 or 5:1) or by recrystallization from EtOH. The two resulting diastereomers could be separated by CSP-HPLC.

4-Formyl[2.2]paracyclophane SAMP-Hydrazones [$R_p$/$S_p$]-2

Following the general procedure GP1, ($R_p$/$S_p$)-2 (1.27 g, 89%) was obtained as an yellow solid from rac-1 (1.00 g, 4.2 mmol) and SAMP (0.53 g, 4.1 mmol). Conditions for HPLC: Chiralpak AD (20 µm, 250 × 50 mm, mobile phase: n-hexane–i-ProOH, 97:3; flow rate: 30 mL/min; t$_{R}$: 19.6 min and 23.4 min). 2.80 g of the diastereomeric mixture afforded 1.24 g (44%) of ($R_p$)-2 and 1.18 g (42%) of ($S_p$)-2.

($S_p$,$S$)-4-Formyl[2.2]paracyclophane SAMP-Hydrazones [$S_p$,$S$]-2

Yield: 1.24 g (39%, after condensation and HPLC); mp 73 °C; [α]$_D^{26}$ = 276.5 (c 1.0, CHCl$_3$).

IR (KBr): 2972 (vs), 2899 (vs), 2860 (vs), 1649 (s), 1602 (s), 1594 (s), 1499 (w), 1480 (w), 1470 (m), 1435 (w), 1395 (w), 1371 (s), 1355 (s), 1267 (w), 1250 (w), 1192 (vs), 1161 (s), 1125 (s), 1095 (s), 1041 (s), 934 (s), 916 (s), 878 (m), 805 (m), 773 (s), 704 (s), 623 (s), 597 (s), 543 (w), 514 (m), 494 cm$^{-1}$ (m).

1H NMR (400 MHz, CDCl$_3$): δ = 1.88–2.11 (m, 4 H, CH$_2$CH$_2$CH$_3$, NCH$_2$CH$_2$), 2.77 (m, 1 H, CH/CH$_2$), 2.89–3.14 (m, 7 H, CH$_2$CH$_2$, CH$_2$CH$_2$, NCH$_2$), 3.45 (s, 3 H, OCH$_3$), 3.49–3.54 (m, 1 H, NCH$_2$), 3.61–3.74 (m, 4 H, CH$_2$O, NCH$_2$CH$_2$), 6.37–6.52 (m, 5 H, ArH), 6.66 (dd, J = 1.7, 7.9 Hz, 1 H, ArH), 6.73 (d, J = 1.4 Hz, 1 H, ArH), 7.22 (s, 1 H, H$_{C=N}$).

13C NMR (100 MHz, CDCl$_3$): δ = 22.15 (NCH$_2$CH$_3$), 26.61 (NCH$_3$), 34.02, 34.52, 35.08, 35.37 (CH$_2$CH$_3$), 49.02 (NCH$_2$), 59.25 (OCH$_3$), 63.21 (NCH$_2$CH$_2$O), 74.55 (CH$_2$O), 129.99, 130.33, 130.77, 131.69, 132.60, 132.66 (C$_{Ar}$), 134.82 (C$_{Ar}$), 136.71, 139.07, 139.09, 139.40 (C$_{Ar}$).

MS (EI): m/z (%) = 324 (M$^+$, 100), 256 (42), 235 (9), 199 (39), 130 (44), 114 (6), 104 (13), 77 (7), 70 (14).

Anal. Calcd for C$_{23}$H$_{28}$N$_2$O: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.76; H, 7.82; N, 8.01.

4-Formyl[2.2]paracyclophane SAMP-Hydrazones [$R_p$/$R_p$]-2

Yield: 1.18 g (37%, after condensation and HPLC); mp 77 °C; [α]$_D^{26}$ = 386.4 (c 1.0, CHCl$_3$).

IR (KBr): 2975 (vs), 2917 (vs), 2836 (vs), 1898 (w), 1728 (w), 1581 (vs), 1499 (vs), 1400 (m), 1428 (w), 1337 (s), 1284 (w), 1186 (vs), 1125 (vs), 1091 (vs), 967 (s), 934 (w), 910 (s), 879 (m), 808 (s), 750 (w), 719 (s), 650 (s), 577 (w), 543 (w), 521 (s), 495 cm$^{-1}$ (s).

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**Figure 1** Crystal structure of the amine ($R_p$)-5a
Flow rate: 30 mL/min; rate: 30 mL/min; AD (20 g, 8.5 mmol). Conditions for HPLC: Chiralpak AD 

(20 g, 41%) (Rp) enantiomer. Yield: 0.78 g (22%, after condensation and HPLC); mp 77 °C; 

All spectroscopic data were consistent with those of the (Rp)-enantiomer.

**4-Formyl[2.2]paracyclophane RAMP-Hydrazone** 

Following the general procedure GP1, (S,R)-2 (2.15 g, 62%) was obtained as a yellow solid from rac-1 (2.36 g, 10.0 mmol) and RAMP (1.68 g, 12.9 mmol). Conditions for HPLC: Chiralpak AD (20 μm, 250 × 50 mm mobile phase: n-hexane–EtOH, 9:1; flow rate: 30 mL/min; tR: 14.7 min and 21.5 min). 2.15 g of the diastereomeric mixture afforded 1.15 g (47%) (Sp)-enantiomer.

**4-Formyl[2.2]paracyclophane RAMBO-Hydrazone**

Following the general procedure GP1. (R/S,R,R)-6 (2.59 g, 79%) was obtained as a yellow solid from rac-1 (2.0 g, 8.5 mmol) and RAMBO (1.4 g, 8.5 mmol). Conditions for HPLC: Chiralpak AD (20 μm, 250 × 50 mm mobile phase: n-hexane–4-PrOH, 97:3; flow rate: 30 mL/min; tR: 13.6 min and 16.6 min). 2.45 g of the diastereomic mixture afforded 1.14 g (47%) (S,R,R,R)-6 and 1.01 g (41%) (R,S,R,R)-6.

Yield: 0.78 g (22%, after condensation and HPLC); mp 77 °C; [α]D25 389.0 (c 1.0, CHCl3).

All spectroscopic data were consistent with those of the (R,S)-enantiomer.

**4-Formyl[2.2]paracyclophane RAMBO-Hydrazone**

Following the general procedure GP1. (R/S,R,R,R)-6 (2.59 g, 79%) was obtained as a yellow solid from rac-1 (2.0 g, 8.5 mmol) and RAMBO (1.4 g, 8.5 mmol). Conditions for HPLC: Chiralpak AD (20 μm, 250 × 50 mm mobile phase: n-hexane–4-PrOH, 97:3; flow rate: 30 mL/min; tR: 13.6 min and 16.6 min). 2.45 g of the diastereomic mixture afforded 1.14 g (47%) (S,R,R,R)-6 and 1.01 g (41%) (R,S,R,R)-6.

Yield: 1.15 g (37%), after condensation and HPLC; mp 138 °C; [α]D20 +310.8 (c 1.0, CHCl3).

IR (KBr): 3037 (w), 3017 (w), 2960 (vs), 2919 (vs), 2845 (vs), 1895 (w), 1572 (s), 1500 (w), 1479 (w), 1436 (s), 1407 (m), 1387 (w), 1332 (s), 1306 (s), 1237 (m), 1174 (vs), 1121 (vs), 1087 (vs), 970 (s), 939 (w) 906 (s), 877 (s), 801 (vs), 721 (vs), 648 (s), 581 (w), 546 (w), 508 cm–1 (s).

**1H NMR (400 MHz, CDCl3); δ = 1.45 (m, 1 H, NCHCH/HCH), 1.60–1.88 (m, 6 H, CHCH/CH2).**

IR (KBr): 3037 (w), 3017 (w), 2960 (vs), 2919 (vs), 2845 (vs), 1895 (w), 1572 (s), 1500 (w), 1479 (w), 1436 (s), 1407 (m), 1387 (w), 1332 (s), 1306 (s), 1237 (m), 1174 (vs), 1121 (vs), 1087 (vs), 970 (s), 939 (w) 906 (s), 877 (s), 801 (vs), 721 (vs), 648 (s), 581 (w), 546 (w), 508 cm–1 (s).

**13C NMR (100 MHz, CDCl3); δ = 24.23 (CH3CH2CH3), 32.26 (NCHCH3CH3), 33.06 (CH3CH2CH2CH3), 34.07 (NCHCH2CH3), 34.49, 34.54, 35.11, 35.36 (CH3CH2), 40.71 (NCHCH), 59.45 (OCH3), 65.43 (NCHCH2O), 66.48 (NCHCH), 75.45 (CH2O), 129.70, 130.84, 131.58, 131.68, 132.70, 132.84 (C=O), 133.82 (C=O), 135.11 (C=O), 135.67, 136.91, 139.10, 139.25, 139.32 (C=O).

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duted pressure and the aqueous solution was basified with aq sat. NaHCO₃. The amines were extracted with CH₂Cl₂ (2 × 10 mL/mmol), the solution was concentrated in vacuo, and the residues were converted into the corresponding benzyl carbamates as follows.

The crude products were dissolved in CH₂Cl₂/H₂O (2:1, 10 mL/mmol) and treated with K₂CO₃ (2.7 equiv) and CbzCl (2.5 equiv). After 72 h reflux, the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL/mmol) and the combined organic layers were washed with brine (10 mL), dried (MgSO₄), and concentrated in vacuo. The benzyl carbamates were obtained as colorless solids after flash column chromatography (SiO₂, n-pentane–EtO–CH₂Cl₂ 1:10:2:2).

**Benzyl (RₓRₓ)-[1-[[2.2]Paracyclophane-4'-yl]ethyl]carbamate ([RₓRₓ]-5a)**

Following the general procedure GP2, the reaction of (RₓRₓ)-2 (0.348 g, 1.0 mmol) with EtLi (3.0 mmol), followed by N–N cleavage and protection with Cbz-Cl gave 0.360 g (93% over three steps) of pure (RₓRₓ)-5a; mp 116 °C; [α]₂⁰⁺ 26.9 (c 1.0, CHCl₃).

IR (KBr): 3330 (vs), 3065 (w), 3032 (m), 3008 (m), 2927 (s), 2852 (m), 1945 (w), 1890 (w), 1691 (vs), 1594 (w), 1535 (vs), 1451 (m), 1411 (w), 1376 (w), 1339 (m), 1286 (m), 1246 (vs), 1136 (w), 1103 (s), 1051 (s), 1021 (s), 938 (m), 804 (m), 858 (w), 824 (w), 798 (w), 774 (w), 745 (m), 717 (w), 697 (m), 651 (m), 602 (w), 569 (w), 501 (w), 481 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.23 (d, J = 6.6 Hz, 3 H, CH₃), 2.84–3.39 (m, 8 H, CH₂CH₂), 5.01–5.04 (m, 2 H, NH, NCH), 5.19 (d, J = 12.1 Hz, 1 H, CHPhH), 5.31 (d, J = 12.1 Hz, 1 H, CHPhH), 6.16–6.77 (m, 7 H, ArH), 7.32–7.48 (m, 5 H, C₆H₅).

13C NMR (100 MHz, CDCl₃); δ = 25.00 (CH₃), 33.67, 34.56, 35.20, 35.24 (CH₂CH₂), 48.12 (NCH), 66.75 (CH₃Ph), 127.30, 128.05, 128.27, 128.42, 131.18, 131.65, 132.34, 132.41, 132.57, 135.44 (C₆H₅), 135.73, 135.66, 135.88, 139.13, 140.02, 141.84 (C₆H₅), 155.37 (C=O).

MS (El 70 eV): m/z (%) = 385 (M⁺, 18), 326 (9), 297 (29), 2853 (m), 1952 (w), 1896 (w), 1685 (vs), 1594 (w), 1538 (vs), 1452 (s), 1412 (w), 1379 (w), 1347 (m), 1261 (vs), 1237 (w), 1137 (w) 1109 (m), 1071 (m), 1035 (s), 970 (s), 903 (m), 859 (w), 827 (w), 799 (w), 780 (w), 750 (m), 699 (s), 649 (w), 605 (w), 518 (w), 483 cm⁻³ (w).

IR (film): 3389 (m), 3326 (m), 3009 (s), 2957 (s), 2925 (s), 2853 (m), 1952 (w), 1896 (w), 1685 (vs), 1594 (w), 1538 (vs), 1452 (s), 1412 (w), 1379 (w), 1347 (m), 1261 (vs), 1237 (w), 1137 (w) 1109 (m), 1071 (m), 1035 (s), 970 (s), 903 (m), 859 (w), 827 (w), 799 (w), 780 (w), 750 (m), 699 (s), 649 (w), 605 (w), 518 (w), 483 cm⁻³ (s).

1H NMR (300 MHz, CDCl₃); δ = 0.81 (t, J = 7.4 Hz, 3 H, CH₃), 1.30–1.67 (m, 2 H, CH₂CH₂), 2.84–3.42 (m, 8 H, CH₂CH₂), 4.89 (m, 1 H, NCH), 5.01 (d, J = 12.4 Hz, 1 H, CHPhH), 5.33 (d, J = 12.4 Hz, 1 H, CHPhH), 6.15–6.75 (m, 7 H, ArH), 7.32–7.49 (m, 5 H, C₆H₅).

13C NMR (75 MHz, CDCl₃); δ = 10.41 (CH₃), 32.05 (CH₂CH₂), 33.29, 34.36, 35.28 (CH₃Ph), 53.64 (NCH), 66.87 (CH₃Ph), 127.98, 128.14, 126.33, 131.86, 131.84, 132.53, 132.78, 135.48 (C₆H₅), 136.40, 136.82, 139.07, 139.45, 140.00, 140.85 (C₆H₅), 156.10 (C=O).

MS (El 70 eV): m/z (%) = 399 (M⁺, 89), 370 (12), 326 (56), 308 (6), 264 (55), 247 (12), 222 (5), 193 (21), 160 (12), 143 (18), 119 (5), 104 (15), 91 (100).

Anal. Calc. for C₇H₇NO₃: C 81.17; H 7.32; N 3.51. Found: C 80.89; H 7.61; N 3.50.

**Benzyl (RₓRₓ)-[1-[[2.2]Paracyclophane-4'-yl]propyl]carbamate ([RₓRₓ]-5b)**

Following the general procedure GP2, the reaction of (RₓRₓ)-2 (0.348 g, 1.0 mmol) with EtLi (3.0 mmol), followed by N–N cleavage and protection with Cbz-Cl gave 0.076 g (63%, over three steps) of pure (RₓRₓ)-5b; mp 116 °C; [α]₂⁰⁺ 26.9 (c 1.0, CHCl₃).

All spectroscopic data were consistent with those of the (RₓRₓ)-enantiomer.

**Benzyl (RₓRₓ)-[1-[[2.2]Paracyclophane-4'-yl]ethyl]carbamate ([RₓRₓ]-5a)**

Following the general procedure GP2, the reaction of (RₓRₓ)-2 (0.174 g, 0.5 mmol) and MeLi (1.5 mmol), followed by N–N cleavage and protection with Cbz-Cl gave 0.166 g (86% over three steps) of pure (RₓRₓ)-5a; mp 116 °C; [α]₂⁰⁺ 26.6 (c 1.0, CHCl₃).

All spectroscopic data were consistent with those of the (RₓRₓ)-enantiomer.

**Benzyl (RₓRₓ)-[1-[[2.2]Paracyclophane-4'-yl]propyl]carbamate ([RₓRₓ]-5b)**

Following the general procedure GP2, the reaction of (RₓRₓ)-2 (0.117 g, 0.3 mmol) with MeLi (0.9 mmol), followed by N–N cleavage and protection with Cbz-Cl gave 0.076 g (63%, over three steps) of pure (RₓRₓ)-5b; [α]₂⁰⁺ 27.1 (c 0.7, CHCl₃).

All spectroscopic data were consistent with those of the (RₓRₓ)-enantiomer.

**Benzyl (RₓRₓ)-[1-[[2.2]Paracyclophane-4'-yl]propyl]carbamate ([RₓRₓ]-5b)**

Following the general procedure GP2, the reaction of (RₓRₓ)-2 (0.117 g, 0.3 mmol) with MeLi (0.9 mmol), followed by N–N cleavage and protection with Cbz-Cl gave 0.076 g (63%, over three steps) of pure (RₓRₓ)-5b; [α]₂⁰⁺ 27.1 (c 0.7, CHCl₃).

All spectroscopic data were consistent with those of the (RₓRₓ)-enantiomer.
Following the general procedure GP2, reaction of \((R,S)-2\) (0.348 g, 1.0 mmol) with \(n\)-BuLi (3.0 mmol), followed by \(N\)-\(N\) cleavage and protection with Cbz-Cl gave 0.393 g (92% over three steps) of pure \((R,R)-5d\); mp 160 °C; \([\alpha]_D^{20}+24.9^\circ\) (c 1.0, CHCl₃).

IR (KBr): 3309 (vs), 3027 (w), 2952 (s), 2929 (s), 2853 (m), 1684 (vs), 1593 (w), 1541 (vs), 1497 (w), 1455 (m), 1413 (m), 1375 (m), 1350 (w), 1285 (w), 1252 (vs), 1212 (w), 1160 (w), 1101 (m), 1081 (w), 1033 (s), 976 (w), 942 (w), 912 (w), 863 (w), 797 (w), 758 (m), 735 (w), 728 (w), 648 (w), 605 (w), 560 (w), 511 (w), 488 cm⁻¹ (w).

\(^1H\) NMR (400 MHz, CDCl₃): \(\delta = 0.83\) (t, J = 6.9 Hz, 3 H, \(CH_3\)), 1.21–1.59 (m, 6 H, \(CH(CH_3)_2CH(CH_3)\)), 2.86–3.41 (m, 8 H, \(CH(CH_3)_2\)), 4.90–4.98 (m, 2 H, NH, NCH), 5.21 (d, J = 12.4 Hz, 1 H, \(CH(=\_\)Ph)), 5.32 (d, J = 12.4 Hz, 1 H, \(CH(=\_\)Ph)), 6.15–6.75 (m, 7 H, ArH), 7.33–7.49 (m, 5 H, \(C_6H_5\)).

\(^13C\) NMR (100 MHz, CDCl₃): \(\delta = 13.99\) (CH₃), 19.17 (CH₃CH₂), 33.26, 34.58, 35.21, 35.25 (CH₂CH₃), 41.39 (CH₃CH₂CH₃), 51.93 (NCH), 66.76 (CH(=\_\)Ph)), 127.69, 128.01, 128.04, 128.26, 128.42, 131.31, 131.59, 132.30, 132.57, 135.27 (C₆H₅), 136.03, 136.59, 138.82, 139.22, 139.82, 141.01 (C₆H₅), 155.76 (C=O).

MS (EL, 70 eV): \(m/z\) (%) = 447 (M⁺, 79), 370 (15), 336 (6), 278 (72), 267 (72), 225 (72), 193 (19), 174 (13), 157 (22), 130 (12), 119 (7), 104 (15), 91 (97).


Benzyl \((R,S,S)-[1-([2.2]Paracyclophane-4'-yl)butyl]carbamate \([1(S)-S]-5c\)^{18}

Mp 164 °C; \([\alpha]_D^{20}+28.4^\circ\) (c 1.0, CHCl₃).

All spectroscopic data were consistent with those of the \((R,R)-\)enantiomer.

Benzyl \((R,S,S)-[1-([2.2]Paracyclophane-4'-yl)pentyl]carbamate \([1(S)-S]-5d\)^{19}

Mp 160 °C; \([\alpha]_D^{20}+26.7^\circ\) (c 1.0, CHCl₃).

All spectroscopic data were consistent with those of the \((R,R)-\)enantiomer.

Benzyl \((R,S,S)-[1-([2.2]Paracyclophane-4'-yl)pentyl]carbamate \([1(S)-S]-5d\)^{19}

Following the general procedure GP2, the reaction of \((R,R,R)-R\) (0.117 g, 0.3 mmol) with \(n\)-BuLi (0.9 mmol), followed by \(N\)-\(N\) cleavage and protection with Cbz-Cl gave 0.048 g (37%, over three steps) of pure \((R,R)-5d\); \([\alpha]_D^{20}=+74.1^\circ\) (c 0.85, CHCl₃).

IR (film): 3384 (s), 3329 (s), 3010 (s), 2930 (vs), 2859 (s), 1952 (w), 1887 (w), 1712 (vs), 1594 (m), 1506 (vs), 1457 (s), 1377 (w), 1326 (w), 1236 (vs), 1099 (s), 1066 (s), 1043 (s), 941 (w), 902 (m), 865 (w), 798 (s), 755 (vs), 699 (s), 652 (w), 515 (m), 495 cm⁻¹ (w).

\(^1H\) NMR (400 MHz, CDCl₃): \(\delta = 1.00\) (t, J = 7.0 Hz, 3 H, \(CH_3\)), 1.44–2.00 (m, 6 H, \(CH(CH_3)_2CH(CH_3)_2\)), 2.76–3.54 (m, 8 H, \(CH(CH_3)_2\)), 4.51 (d, J = 9.6 Hz, 1 H, NH), 4.75 (dt, J = 3.8, 9.6 Hz, 1 H, NCH), 5.07 (d, J = 12.4 Hz, 1 H, \(CH(=\_\)Ph)), 5.15 (d, J = 12.4 Hz, 1 H, \(CH(=\_\)Ph)), 6.31–6.53 (m, 7 H, ArH), 7.32 (br s, 5 H, \(C_6H_5\)).

\(^13C\) NMR (100 MHz, CDCl₃): \(\delta = 14.21\) (CH₃), 22.87 (CH₃CH₂), 28.48 (CH₃CH₂CH₃), 33.55, 33.67 (CH₃CH₂CH₃), 34.62, 35.12, 35.24 (CH₂CH₃), 51.74 (NCH), 66.50 (CH₃), 127.72, 127.79, 128.25, 129.52, 129.77, 131.73, 131.94, 132.74, 133.18, 135.52 (C₆H₅), 136.52, 138.98, 139.10, 139.48, 139.73, 140.30 (C₆H₅), 155.81 (C=O).

MS (EL, 70eV): \(m/z\) (%) = 427 (M⁺, 60), 370 (10), 326 (90), 292 (96), 275 (17), 262 (6), 236 (7), 222 (10), 193 (20), 188 (16), 171 (24), 130 (21), 119 (90), 104 (18), 91 (100).
Benzylic (R,R)-[1-{[2.2]Paracyclophane-4′-yl]-2,2-dimethylpropyl} carbamate [((R,R)-5e]

Following the general procedure GP2, the reaction of (R,R,S)-2 (0.349 g, 1.0 mmol) with t-BuLi (3.0 mmol), followed by N–N cleavage and protection with Cbz-Cl gave 0.244 g (57% over three steps) of pure (R,R)-5e; mp 85 °C; [α]D°20 +8.1 (c 1.0, CHCl3).

IR (KBr): 3334 (m), 3064 (w), 3031 (m), 3009 (w), 2950 (vs), 2866 (s), 1989 (w), 1694 (3.16), 1595 (w), 1536 (vs), 1458 (w), 1412 (w), 1395 (w), 1365 (m), 1344 (m), 1231 (vs), 1182 (w), 1133 (w), 1099 (w), 1082 (m), 1045 (s), 1006 (s), 938 (w), 902 (w), 866 (w), 799 (w), 777 (w), 739 (m), 718 (w), 698 (m), 641 (w), 584 (w), 512 (w), 462 cm−1 (w).

1H NMR (400 MHz, CDCl3): δ = 0.86 (t, J = 6.7 Hz, 3 H, CH3), 1.03–1.99 (m, 3 H, CH2CH2), 2.78–3.55 (m, 8 H, CH2CH2), 3.86 (d, J = 10.7 Hz, 1 H, NCH), 5.19 (d, J = 12.1 Hz, 1 H, CH2Ph), 5.31 (d, J = 12.1 Hz, 1 H, CH2Ph), 5.41 (d, J = 10.7 Hz, 1 H, NH), 6.07–6.52 (m, 7 H, ArH), 7.28–7.51 (m, 5 H, C6H5). All spectroscopic data were consistent with those of the (R,R)-enantiomer.

Anal. Calcd for C29H33NO2: C, 81.46; H, 7.78; N, 3.28. Found: C, 81.34; H, 7.54; N, 3.20.

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References


(12) CCDC 673149 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing to data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033.


(17) For an alternative synthesis starting from (R)-4-formyl[2,2]-paracyclophane N,N-dimethylhydrazone, see ref. 7.

(18) The preparation of this enantiomer was described in a preceding communication, see ref. 7.