Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Unprecedented pseudo-*ortho* and *ortho* metallation of [2.2]paracyclophanes – a methyl group matters

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CONTENTS

1. EXPERIMENTAL PROCEDURES

General. The starting materials, solvents and reagents were purchased from Acros, ABCR, Alfa Aesar or Sigma-Aldrich and used without further purification. All reactions involving moisture sensitive reactants were executed under argon atmosphere using oven dried or flame dried glassware. Dry *n*hexane, dry cyclohexane and dry diethylether were distilled from sodium under argon using benzophenone as indicator prior to use. TLC: MERCK ready-to-use plates with silica gel 60 (F254). Column chromatography: MERCK silica gel 60 (0.04–0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on a *Bruker* Avance 400 [400 MHz (^{1}H) and 100 MHz (^{13}C)] and a *Bruker* Avance DRX 500 [500 MHz (^{1}H) and 125 MHz (^{13}C)] spectrometer. All spectra are referenced to tetramethylsilane (TMS) as the internal standard (δ = 0 ppm) by using the signals of the residual protons of $CHCl_3$ [7.26 ppm (^{1}H) or 77.0 ppm (^{13}C)] in $CDCl_3$. Multiplicities of signals are described as follows: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets. Coupling constants (*J*) are given in Hertz (Hz). Mass spectra (EI and HRMS) were measured on a Finnigan MAT 90 spectrometer or on an Agilent GC-MS (GC 6890N, MS 5975B VL MSD) (GC-MS). IR (infrared spectroscopy) spectra were recorded on a FT-IR *Bruker* IFS 88 or a *Bruker* Alpha T spectrometer. IR spectra were recorded using the DRIFT technique (diffused reflectance infrared Fourier transform-spectroscopy) or ATR Diamond (attenuated total reflection) for solids. IR spectra of oils were determined as KBr plates, prepared inside an argon atmosphere. The deposit of the absorption band was given in wave numbers $\tilde{\nu}$ in cm^{-1}. Analytical HPLC (reversed phase) was performed using Agilent Series 1100, equipped with a C18 PerfectSil Target (ODS-3-5 µm, 4.0 × 250 mm, flow rate: 1 mL/min). Preparative HPLC (reversed phase) was performed using Jasco, equipped with C18 Vydac 218TP Series target (22 mm x 250 mm), MD210 plus multi wavelength detector, PU-2087 plus pump, CO-2060 plus thermostat and CHF-122sc fraction assembler (flow rate: 15 mL/min).

Synthesis of both diastereomers (R_p,*R*)/(S_p,*S*)-1-([2.2]paracyclophane-4-yl)-*N*,*N*-(dimethyl)ethylamine ((R_p,*R*)/(S_p,*S*)-**2**) and (R_p,*S*)/(S_p,*R*)-1-([2.2]paracyclophane-4-yl)-*N*,*N*-(dimethyl)ethylamine ((R_p,*S*)/(S_p,*R*)-**2**), **method A**:

In a Schlenk flask under argon atmosphere, lithium perchlorate (255 mg, 0.600 equiv., 2.40 mmol) was dissolved in 10 mL dry dichloromethane. After stirring for 5 minutes, formyl[2.2]paracyclophane (1.00 g, 1.00 equiv., 4.24 mmol, **1**). After further 20 minutes, dimethylamine (2 M in tetrahydrofuran, 3.18 mL, 1.50 equiv., 6.30 mmol) was added and the solution was stirred for 2 hours. Then, methylmagnesium iodide (3 M in tetrahydrofuran, 4.20 mL, 3.00 equiv., 12.6 mmol) was added at 0 °C and the mixture was stirred for 3 hours at this temperature. The reaction was hydrolysed with 10 mL water and the aqueous phase was extracted with chloroform (3 × 20 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified via column chromatography (cyclohexane/ethyl acetate 1:1, ethyl acetate, ethyl acetate + 5% NEt_3) to yield (R_p,*R*)/(S_p,*S*)-**2** (310 mg, 1.11 mmol, 26%) and (R_p,*S*)/(S_p,*R*)-**2** (308 mg, 1.11 mmol, 26%), both as colorless solids.

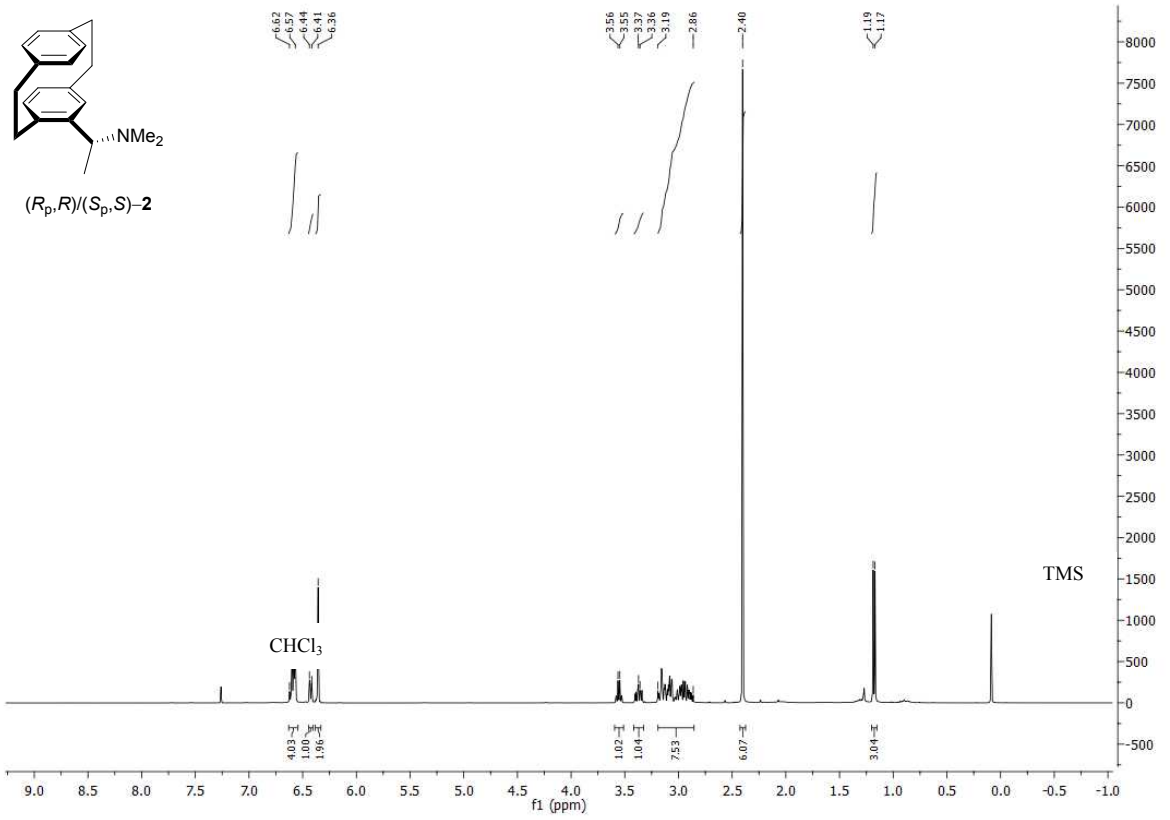
Synthesis of diastereomer (R_p,*R*)/(S_p,*S*)-1-([2.2]paracyclophane-4-yl)-*N*,*N*-(dimethyl)ethylamine ((R_p,*R*)/(S_p,*S*)-**2**), **method B**:

In an high pressure reaction vessel, (*rac*)-4-acetyl[2.2]paracyclophane (2.00 g, 1.00 equiv., 7.99 mmol, **3**) was suspended in 10 mL of an $HNMe_2$ solution (5.6 M in ethanol) under argon atmosphere. Then, $Ti(O\textit{i}Pr)_4$ (4.50 mL, 1.84 equiv., 14.7 mmol) was slowly added. The mixture was stirred for 16 h at 80 °C and afterwards cooled down to room temperature. The suspension was transferred into a Schlenk flask and 80 mL methanol were added. Then, the solution was cooled down to 0 °C and sodium borohydride (454 mg, 1.50 equiv., 12.0 mmol) was slowly added. After 10 minutes at 0 °C, the reaction was allowed to warm up to room temperature and stirred for further 5 hours. The mixture was hydrolysed with water and the solvent evaporated under reduced pressure. The residue was dissolved in 200 mL water and 150 mL dichloromethane. Phases were separated overnight. The aqueous phase was extracted with dichloromethane (3 × 150 mL) and the combined organic phases were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude was purified via column chromatography (ethyl acetate) to yield a colorless solid (1.86 g, 6.63 mmol, 83%).

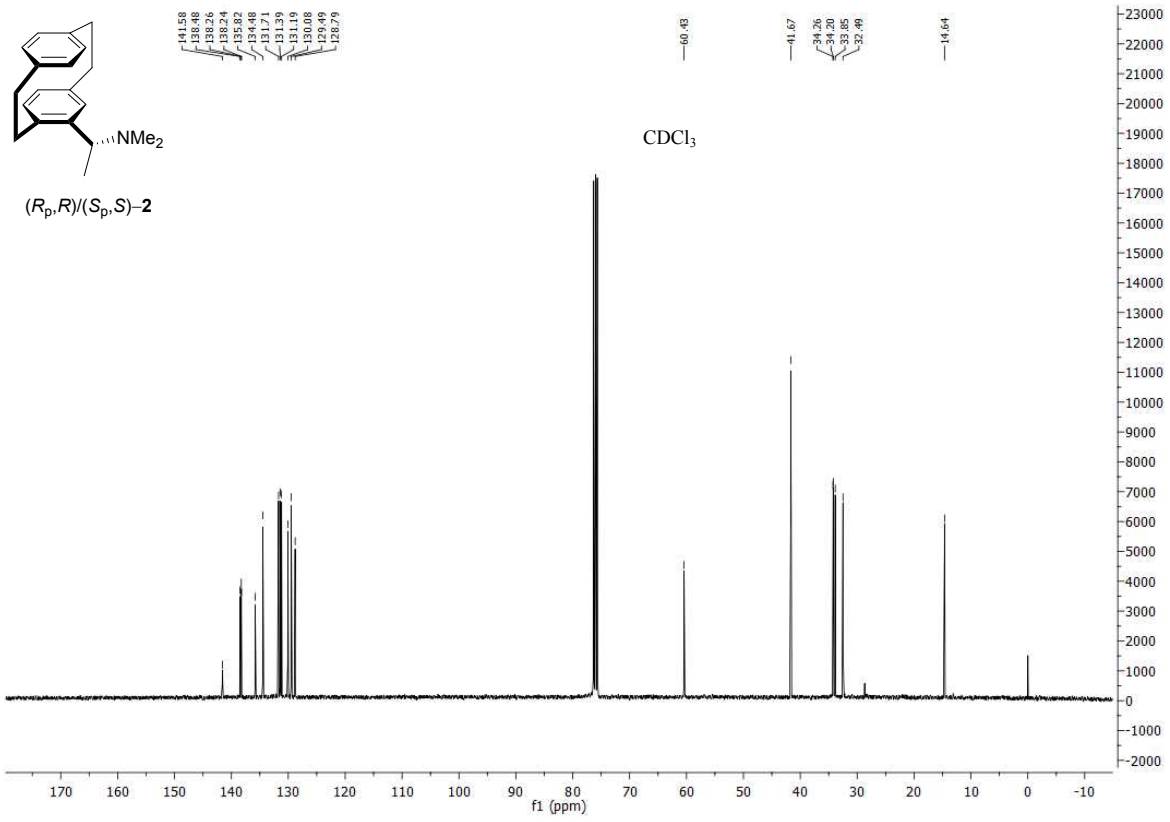
Analytical data were measured for diastereomer (R_p,*R*)/(S_p,*S*)-**2**.

R_f = 0.17 (cyclohexane/ethyl acetate 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64–6.56 (m, 4 H, Pc-H_{Ar}), 6.42 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.6 Hz, 1 H, Pc-H_{Ar}), 6.36 (s, 2 H, Pc-H_{Ar}), 3.56 (q, $^3J_{HH}$ = 6.9 Hz, 1 H, C*H*CH_3), 3.37 (ddd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 4.5 Hz, 1 H, H_{Pc}), 3.19–2.86 (m, 7 H, H_{Pc}), 2.40 (s, 6 H, N(CH_3)$_2$), 1.18 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6 (C_{quart}, C_{Ar}), 138.5 (C_{quart}, C_{Ar}), 138.3 (C_{quart}, C_{Ar}), 138.2 (C_{quart}, C_{Ar}), 135.8 (C_{quart}, C_{Ar}), 134.5 (+, C_{Ar}H), 131.7 (+, C_{Ar}H), 131.4 (+, C_{Ar}H), 131.2 (+, C_{Ar}H), 130.1 (+, C_{Ar}H), 129.5 (+, C_{Ar}H), 128.8 (+, C_{Ar}H), 60.4 (+, *C*HCH_3), 41.7 (+, N(*C*H_3)$_2$), 34.3 (–, *C*H_2), 34.2 (–, *C*H_2), 33.9 (–, *C*H_2), 32.5 (–, *C*H_2), 14.6 (+, CH*C*H_3) ppm. IR (ATR) δ = 2933 (m), 1590 (w), 1459 (w), 1371 (w), 1263 (w), 1114 (m), 906 (w), 863 (w), 801 (w), 718 (w), 627 (w), 516 (w) cm^{-1}. MS (70 eV, EI), m/z (%): 279 (100) [M^+], 264 (79) [M^+–CH_3], 236 (33) [M^+–C_2H_5N], 219 (25) [M^+–$C_3H_{10}N$], 175 (334) [M^+–C_8H_8], 160 (43) [M^+–C_9H_{11}], 131 (51) [M^+–$C_{10}H_{14}N$], 117 (30) [$C_9H_9^+$], 72 (42) [$C_4H_{10}N^+$]. HRMS ($C_{20}H_{25}N$): calc. 279.1987, found 279.1990.

^{1}H NMR (400 MHz, $CDCl_3$) of (R_p,R)/(S_p,S)-**2**:



^{13}C NMR (100 MHz, $CDCl_3$) of (R_p,R)/(S_p,S)-**2**:

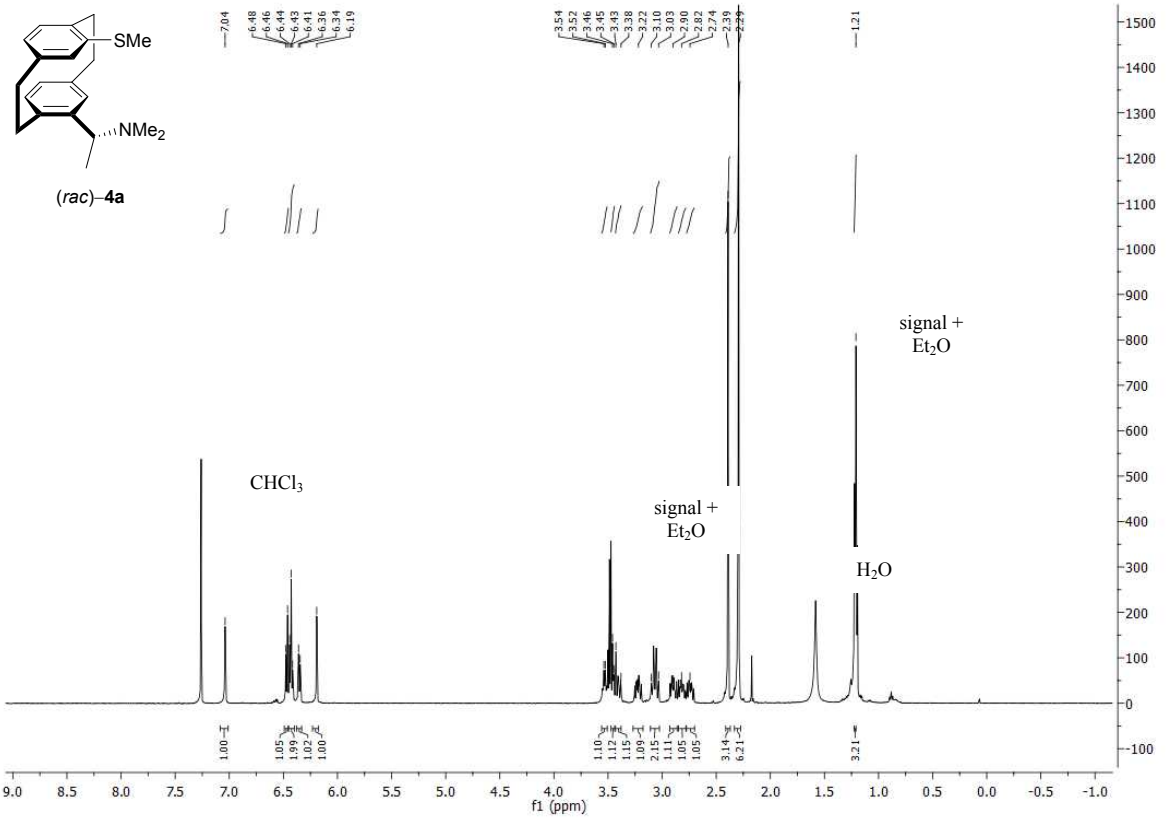


Synthesis of (R_p,*R*)/(S_p,*S*)-1-(4-methylsulfanyl-[2.2]paracyclophane-16-yl-*N*,*N*-(dimethyl)ethylamine ((R_p,*R*)/(S_p,*S*)-**4a**):

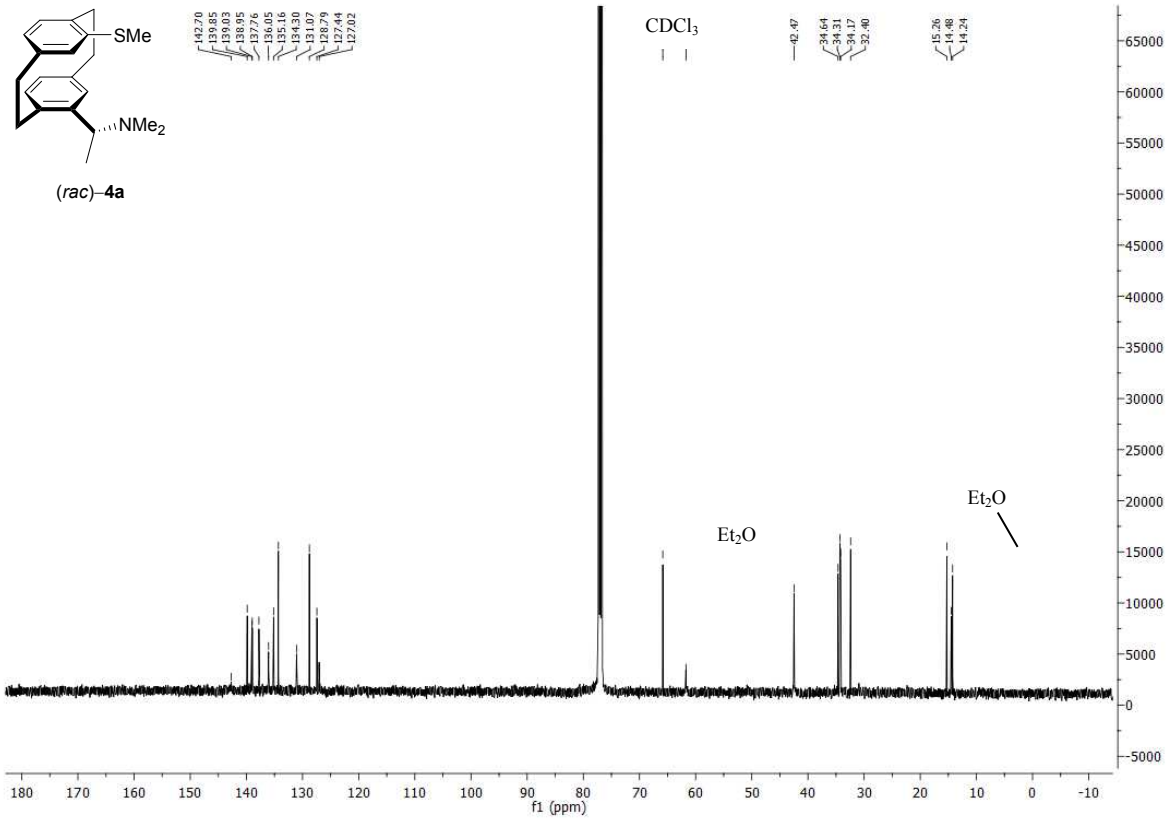
In a high pressure vessel, (R_p,*R*)/(S_p,*S*)-**2** (200 mg, 1.00 equiv., 0.716 mmol) was dissolved in 4 mL of dry cyclohexane. *s*BuLi (1.3 M in cyclohexane/hexane 92:8, 1.65 mL, 3.00 equiv., 2.15 mmol) was added and the solution was stirred for 24 h at 35 °C. Then, the mixture was diluted with 4 mL of dry hexane, cooled down to –78 °C and treated with dimethyl disulfide (0.382 mL, 6.00 equiv., 4.30 mmol). The reaction was allowed to warm up to room temperature within 5 hours and was stirred overnight. The following day, 2 mL of diethylether were added and the organic phase was washed with water first and was then extracted with 1 M HCl (3 × 10 mL). The combined aqueous phases were neutralized upon addition of an aqueous, 4 M KOH solution and then extracted with diethylether (3 × 20 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product (202 mg) was a mixture of product and starting material with a ratio of 83:17 which could only be purified via preparative HPLC (5–99% acetonitril in water for 30 min, 35 °C) to yield a colorless solid (133 mg, 0.409 mmol, 54%).

Retention time (5–95% acetonitrile in water for 30 min, 25 °C): 18.8 min, 96% purity. R_f = 0.65 (hexane/diethylether 5:1 + 5% NEt_3). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.04 (s, 1 H, Pc-H_{Ar}-5), 6.47 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, Pc-H_{Ar}-16), 6.44 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, Pc-H_{Ar}-8), 6.42 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, Pc-H_{Ar}-15), 6.35 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, Pc-H_{Ar}-7), 6.19 (s, 1 H, Pc-H_{Ar}-13), 3.53 (q, ^3J = 6.9 Hz, 1 H, C*H*CH_3), 3.46–3.45 (m, 1 H, H_{Pc}-10), 3.43–3.38 (m, 1 H, H_{Pc}-2), 3.22 (ddd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 7.4 Hz, 1 H, H_{Pc}-9), 3.10–3.03 (m, 2 H, H_{Pc}-1, H_{Pc}-9), 2.90 (ddd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 7.1 Hz, 1 H, H_{Pc}-1), 2.82 (ddd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 7.1 Hz, 1 H, H-2), 2.74 (ddd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 7.4 Hz, 1 H, H_{Pc}-10), 2.39 (s, 3 H, SCH_3), 2.29 (s, 6 H, N(CH_3)$_2$), 1.21 (d, $^3J_{HH}$ = 7.0 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.7 (C_{quart}, C_{Ar}), 139.9 (C_{quart}, C_{Ar}), 139.0 (C_{quart}, C_{Ar}), 138.9 (C_{quart}, C_{Ar}), 137.8 (C_{quart}, C_{Ar}), 136.1 (C_{quart}, C_{Ar}), 135.2 (+, C_{Ar}H), 134.3 (+, C_{Ar}H), 131.1 (+, C_{Ar}H), 128.8 (+, C_{Ar}H), 127.4 (+, C_{Ar}H), 127.0 (+, C_{Ar}H), 61.7 (+, *C*HNMe_2), 42.5 (+, N(CH_3)$_2$), 34.6 (–, CH_2), 34.3 (–, CH_2), 34.2 (–, CH_2), 32.4 (–, CH_2), 14.5 (+, SCH_3), 14.2 (+, CHCH_3) ppm. MS (70 eV, EI), m/z (%): 325 (100) [M^+], 310 (76) [M^+–CH_3], 280 (28) [M^+–$HNMe_2$], 265 (10) [M^+–C_2H_4S], 175 (43) [M^+–$C_9H_{10}S$], 160 (36) [$C_{11}H_{14}N^+$], 151 (26) [M^+–$C_{12}H_{16}N$], 131 (30) [$C_{10}H_{11}^+$], 117 (20) [$C_9H_9^+$], 104 (10) [$C_8H_8^+$]. HRMS ($C_{21}H_{27}NS$): calc. 325.1864, found 325.1862.

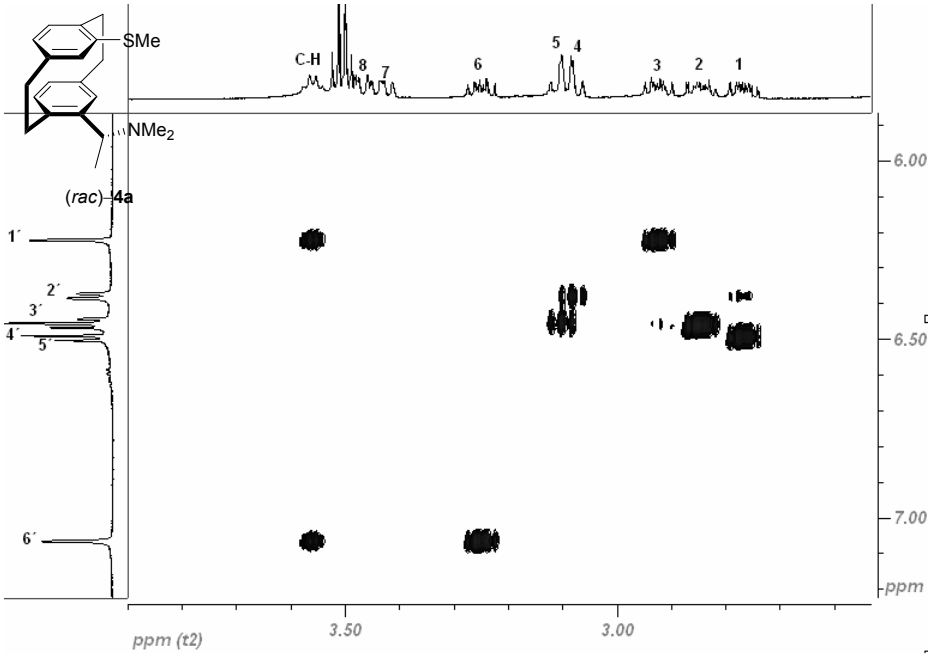
^{1}H NMR (500 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4a**:



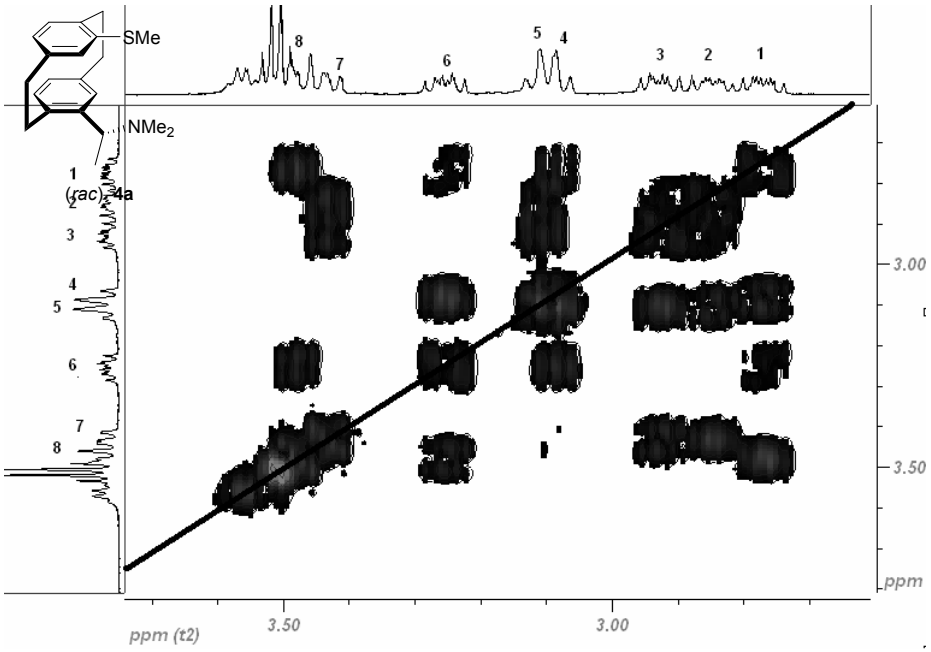
^{13}C NMR (125 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4a**:



^{1}H,^{1}H NOESY-NMR (600 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4a**:



^{1}H,^{1}H COSY-NMR (400 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4a**:

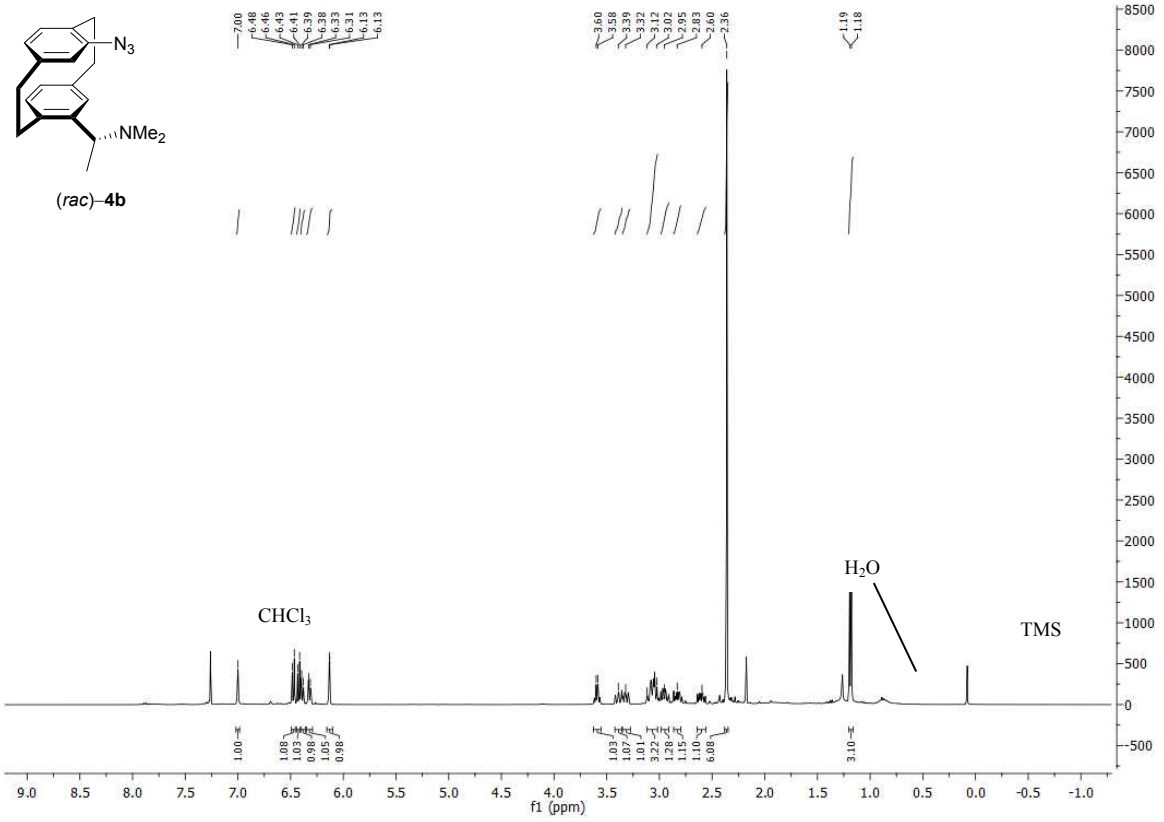


Synthesis of (R_p,*R*)/(S_p,*S*)-1-(4-azido-[2.2]paracyclophane-16-yl-*N*,*N*-(dimethyl)ethylamine ((R_p,*R*)/(S_p,*S*)-**4b**):

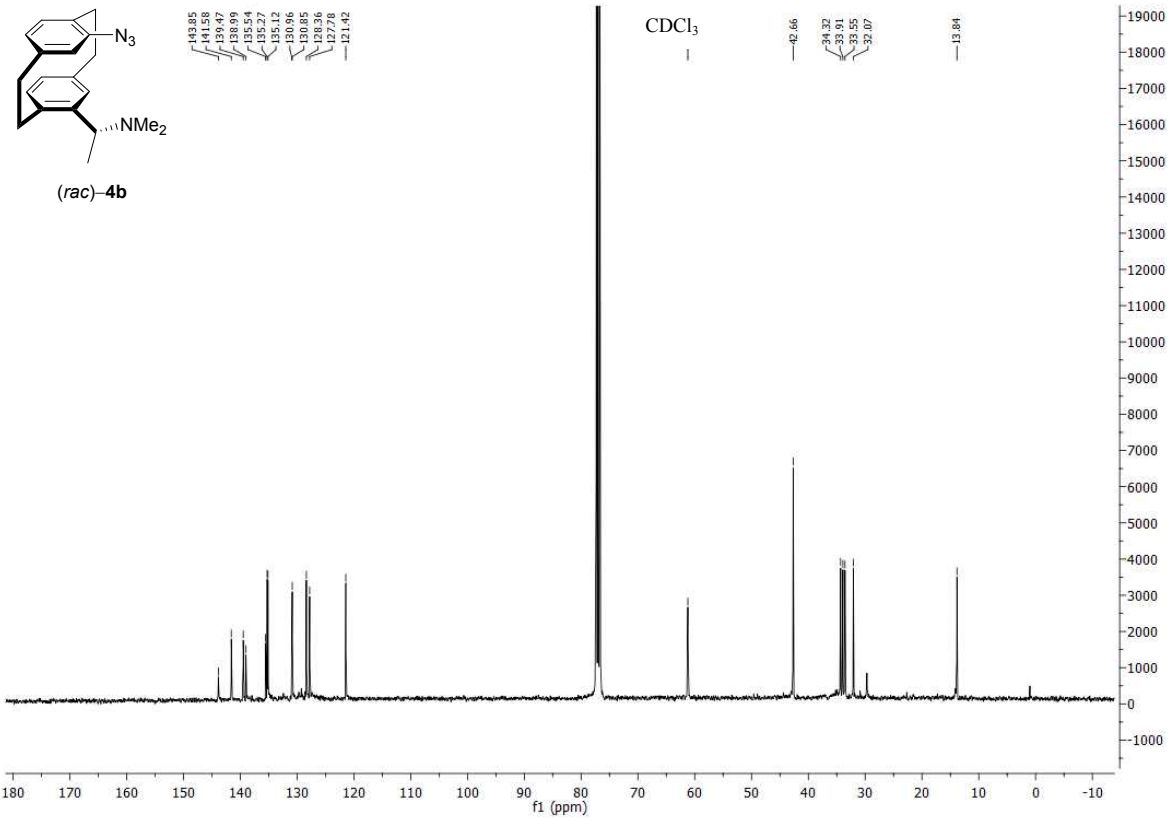
In a Schlenk flask, (R_p,*R*)/(S_p,*S*)-**2** (200 mg, 1.00 equiv., 0.716 mmol) was dissolved in 8 mL of dry cyclohexane. *s*BuLi (1.3 M in cyclohexane/hexane 92:8, 1.65 mL, 3.00 equiv., 2.15 mmol) was added and the solution was stirred for 44 h at 35 °C. Then, the mixture was diluted with 8 mL of dry hexane, cooled down to –78 °C and treated with tosyl azide (592 mg, 6.00 equiv., 4.19 mmol). The reaction was allowed to warm up to room temperature within 5 hours and was stirred overnight. The following day, 10 mL of a 6 M KOH solution were added and the mixture was stirred for further 10 minutes. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified via column chromatography (cyclohexane/acetone 2:1) to yield an orange solid (108 mg, 0.338 mmol, 47%).

R_f = 0.38 (cyclohexane/acetone 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (bs, 1 H, Pc-H_{Ar}), 6.47 (d, $^3J_{HH}$ = 7.8 Hz, 1 H, Pc-H_{Ar}), 6.42 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, Pc-H_{Ar}), 6.39 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz, 1 H, Pc-H_{Ar}), 6.32 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.8 Hz, 1 H, Pc-H_{Ar}), 6.13 (d, $^4J_{HH}$ = 1.5 Hz, 1 H, Pc-H_{Ar}), 3.59 (q, $^3J_{HH}$ = 6.8 Hz, 1 H, C*H*NMe$_2$), 3.39 (ddd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 1.7 Hz, 1 H, H_{Pc}), 3.32 (ddd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 2.2 Hz, 1 H, H_{Pc}), 3.12–3.02 (m, 3 H, H_{Pc}), 2.95 (ddd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 1.6 Hz, 1 H, H_{Pc}), 2.83 (ddd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 6.8 Hz, 1 H, H_{Pc}), 2.60 (ddd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 7.2 Hz, 1 H, H_{Pc}), 2.36 (s, 6 H, N(C*H*$_3$)$_2$), 1.19 (d, $^3J_{HH}$ = 6.8 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9 (C_{quart}, C_{Ar}), 141.6 (C_{quart}, C_{Ar}), 139.5 (C_{quart}, C_{Ar}), 139.0 (C_{quart}, C_{Ar}), 135.5 (C_{quart}, C_{Ar}), 135.3 (+, C_{Ar}H), 135.1 (+, C_{Ar}H), 131.0 (C_{quart}, C_{Ar}), 130.9 (+, C_{Ar}H), 128.4 (+, C_{Ar}H), 127.8 (+, C_{Ar}H), 121.4 (+, C_{Ar}H), 61.2 (+, *C*HNMe$_2$), 42.7 (+, N(*C*H$_3$)$_2$), 34.3 (–, *C*H$_2$), 33.9 (–, *C*H$_2$), 33.6 (–, *C*H$_2$), 32.1 (–, *C*H$_2$), 13.8 (+, CH*C*H$_3$) ppm. IR (ATR) δ = 2935 (m), 2821 (m), 2780 (m), 2115 (n), 1561 (m), 1458 (m), 1410 (m), 1289 (m), 1178 (w), 1046 (w), 908 (w), 870 (w), 777 (w), 731 (w), 651 (w), 528 (w), 492 (w) cm^{-1}. MS (70 eV, EI), m/z (%): 320 (100) [M$^+$], 315 (38) [M$^+$ –CH$_3$], 279 (30) [MH$^+$ –N$_3$], 277 (36) [M$^+$ –C$_2$H$_5$N], 248 (19) [C$_{16}$H$_{14}$N$_3^+$], 234 (28) [C$_{18}$H$_{18}^+$], 175 (26) [M$^+$ – C$_8$H$_7$N$_3$], 160 (21) [C$_{11}$H$_{14}$N$^+$], 145 (19) [C$_8$H$_7$N$_3^+$], 131 (44) [C$_{10}$H$_{11}^+$], 117 (30) [C$_9$H$_9^+$] , 104 (21) [C$_8$H$_8^+$]. HRMS (C$_{20}$H$_{24}$N$_4$): calc. 320.2001, found 320.2003.

^{1}H NMR (400 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4b**:



^{13}C NMR (100 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4b**:

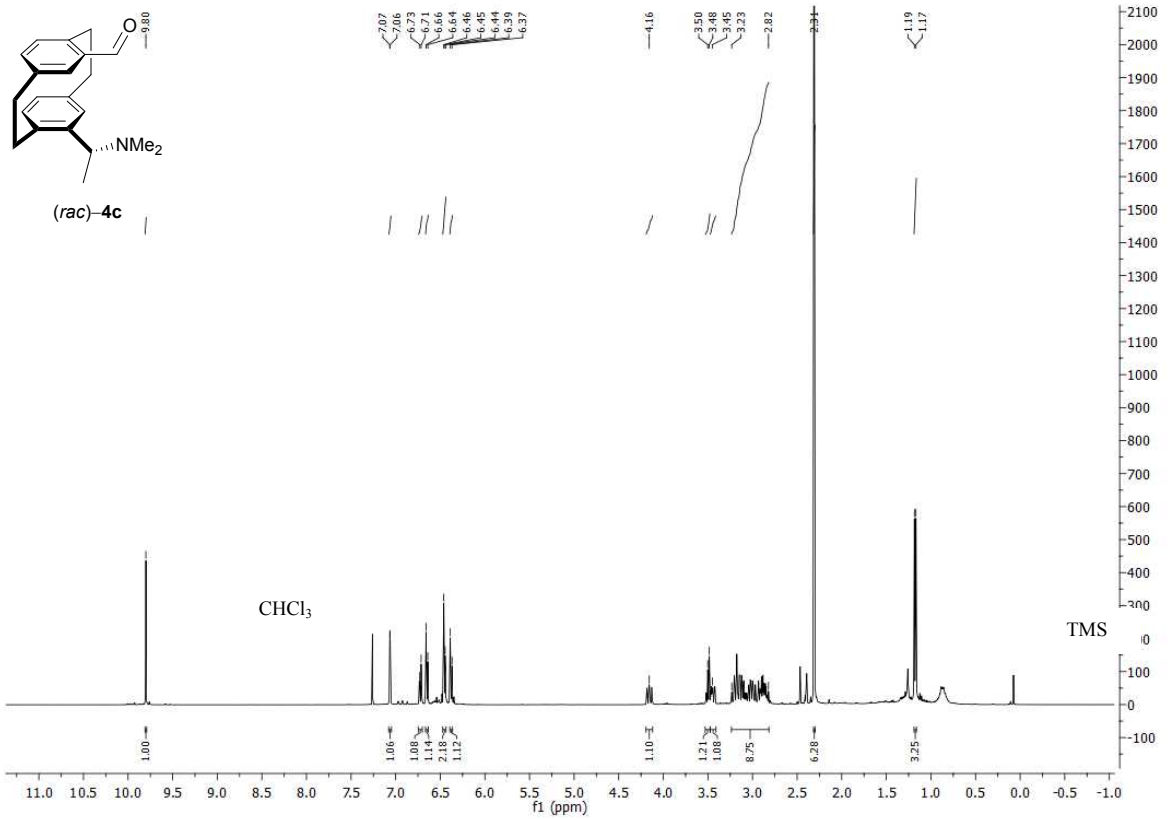


Synthesis of (R_p,*R*)/(S_p,*S*)-1-(4-formyl-[2.2]paracyclophane-16-yl-*N*,*N*-(dimethyl)ethylamine ((R_p,*R*)/(S_p,*S*)-**4c**):

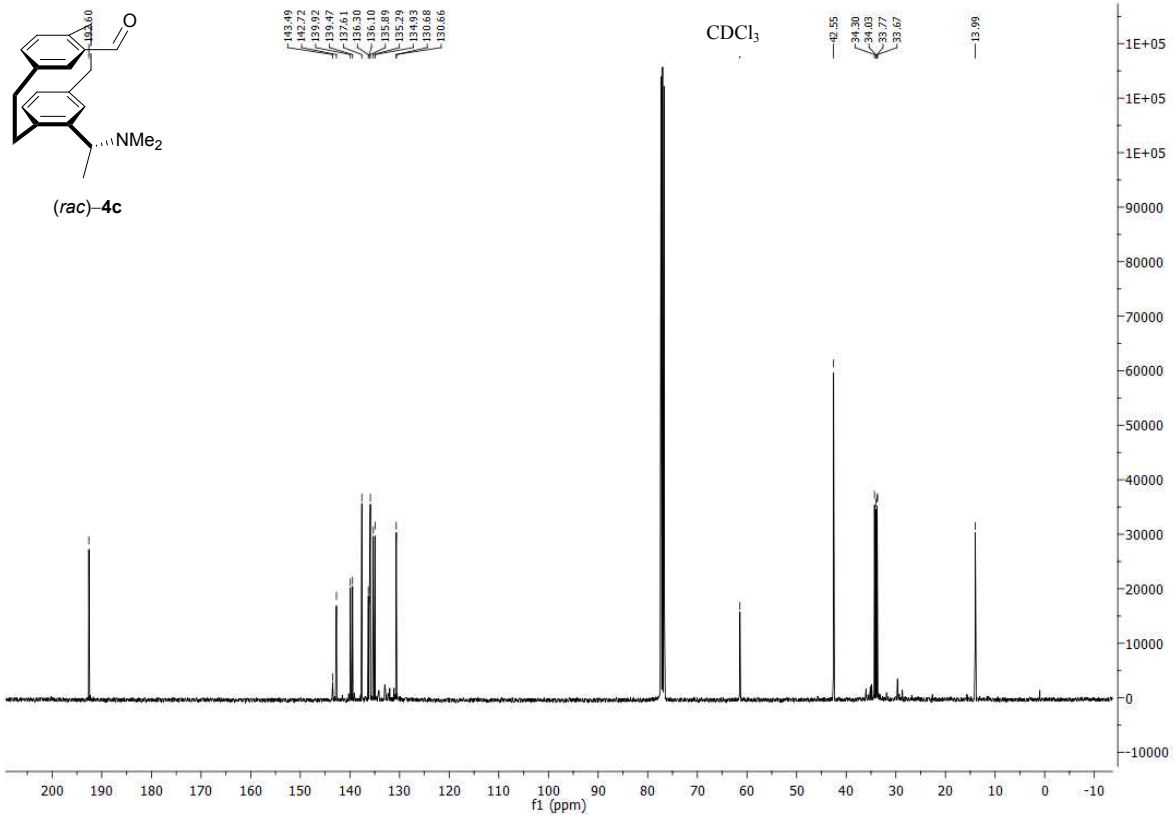
In a Schlenk flask, (R_p,*R*)/(S_p,*S*)-**2** (115 mg, 1.00 equiv., 0.412 mmol) was dissolved in 4 mL of dry cyclohexane. *s*BuLi (1.3 M in cyclohexane/hexane 92:8, 1.90 mL, 5.88 equiv., 2.48 mmol) was added and the solution was stirred for 24 h at 35 °C. Then, the mixture was diluted with 4 mL of dry hexane, cooled down to –78 °C and treated with dimethylformamide (0.360 mL, 12.0 equiv., 4.94 mmol). The reaction was allowed to warm up to room temperature within 5 hours and was stirred overnight. The following day, 20 mL of water were added and the mixture was acidified with 1 M HCl. The aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified via column chromatography (hexane/diethylether 10:1 +5% NEt_3) to yield a colorless solid (60.0 mg, 0.194 mmol, 47%).

R_f = 0.56 (hexane/diethylether 5:1 +5% NEt_3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (s, 1 H, C*H*O), 7.06 (d, $^4J_{HH}$ = 1.9 Hz, 1 H, Pc-H_{Ar}), 6.72 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.9 Hz, 1 H, Pc-H_{Ar}), 6.65 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, Pc-H_{Ar}), 6.45–6.44 (m, 2 H, Pc-H_{Ar}), 6.38 (d, $^3J_{HH}$ = 8.2 Hz, 1 H, Pc-H_{Ar}), 4.16 (ddd, $^2J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 1.2 Hz, 1 H_{Pc}), 3.49 (q, $^3J_{HH}$ = 6.6 Hz, 1 H, C*H*CH_3), 3.45 (ddd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 2.0 Hz, 1 H, H_{Pc}), 3.23–2.82 (m, 6 H, H_{Pc}), 2.31 (s, 6 H, N(CH_3)$_2$), 1.18 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.6 (C_{quart}, *C*HO), 143.5 (C_{quart}, C_{Ar}), 142.7 (C_{quart}, C_{Ar}), 139.9 (C_{quart}, C_{Ar}), 139.5 (C_{quart}, C_{Ar}), 137.6 (+, C_{Ar}H), 136.3 (C_{quart}, C_{Ar}), 136.1 (C_{quart}, C_{Ar}), 135.9 (+, C_{Ar}H), 135.3 (+, C_{Ar}H), 134.9 (+, C_{Ar}H), 130.7 (+, C_{Ar}H), 130.7 (+, C_{Ar}H), 61.4 (+, *C*HNMe_2), 42.6 (+, N(*C*H_3)$_2$), 34.3 (–, *C*H_2), 34.0 (–, *C*H_2), 33.8 (–, *C*H_2), 33.7 (–, *C*H_2), 14.0 (+, CH*C*H_3) ppm. IR (ATR) δ = 2929 (w), 1686 (w), 1383 (w) cm^{-1}. MS (70 eV, EI), m/z (%): 307 (45) [M^+], 292 (80) [M^+ –CH_3], 250 (43) [$C_{18}H_{20}N^+$], 160 (41) [$C_{11}H_{14}N^+$], 146 (52) [$C_{10}H_{12}N^+$], 131 (43) [$C_9H_7O^+$], 104 (21) [$C_8H_8^+$]. HRMS ($C_{21}H_{25}NO$): calc. 307.1936, found 307.1939.

^{1}H NMR (400 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4c**:



^{13}C NMR (100 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4c**:

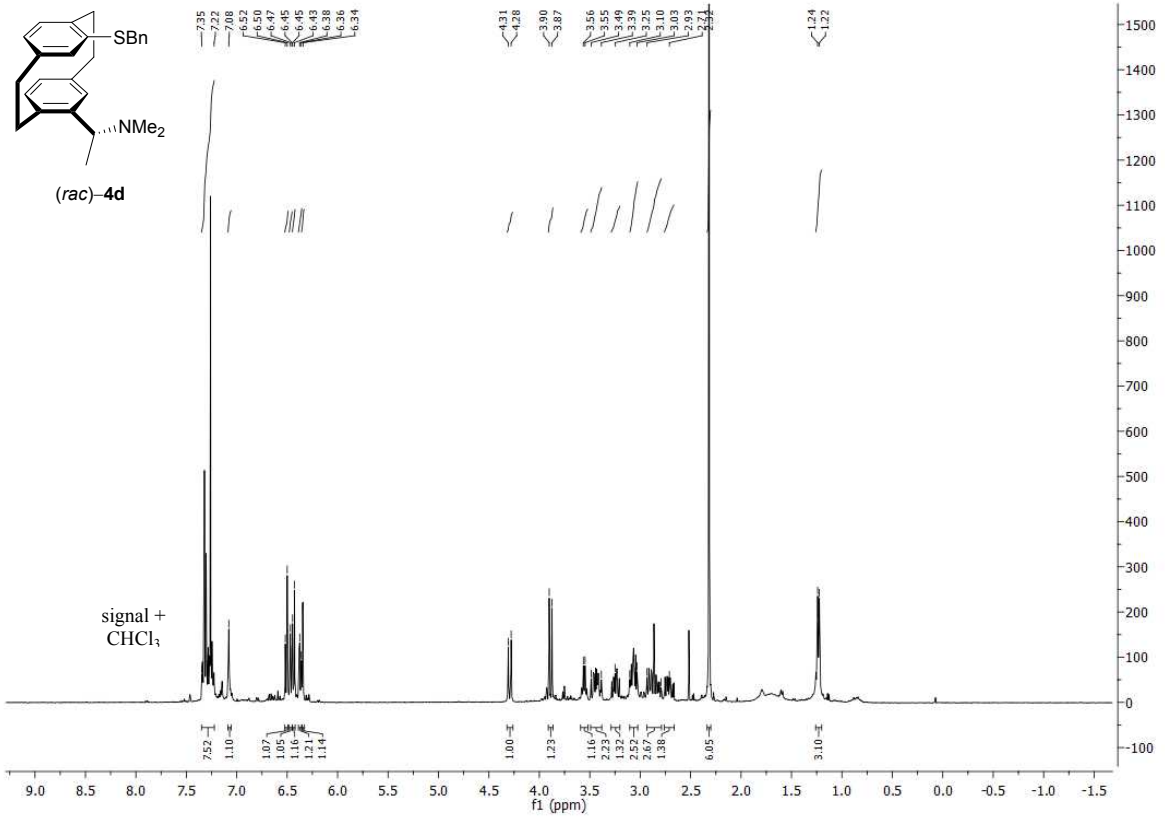


Synthesis of (R_p,*R*)/(S_p,*S*)-1-(4-benzylsulfanyl-[2.2]paracyclophane-16-yl-*N*,*N*-(dimethyl)ethylamine ((R_p,*R*)/(S_p,*S*)-**4d**):

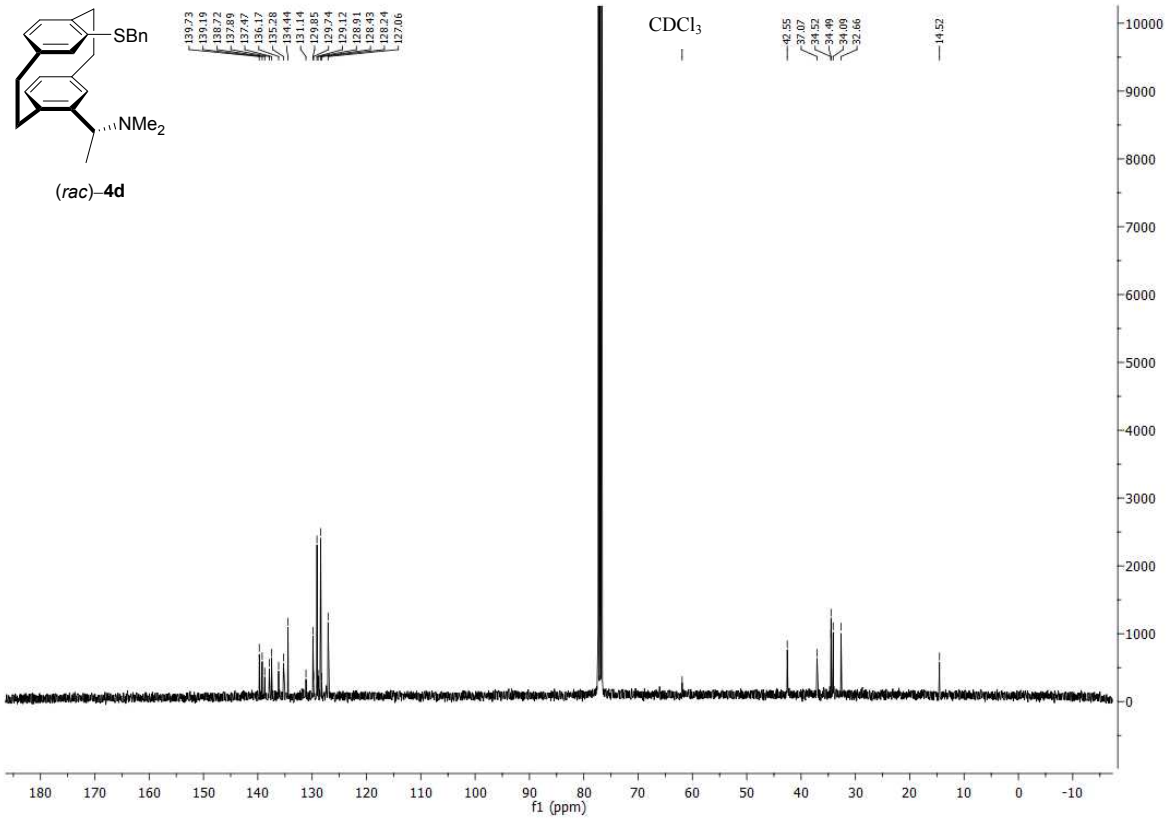
In a Schlenk flask, (R_p,*R*)/(S_p,*S*)-**2** (103 mg, 1.00 equiv., 0.369 mmol) was dissolved in 4 mL of dry cyclohexane. *s*BuLi (1.3 M in cyclohexane/hexane 92:8, 0.85 mL, 3.00 equiv., 1.11 mmol) was added and the solution was stirred for 24 h at 35 °C. Then, the mixture was diluted with 4 mL of dry hexane, cooled down to –78 °C and treated with dimethylformamide (370 mg, 4.05 equiv., 1.50 mmol). The reaction was allowed to warm up to room temperature within 5 hours and was stirred overnight. The following day, the mixture was diluted with 10 mL of diethylether, then washed with water (1 × 5 mL) and finally the organic phase was extracted with 1 M HCl (3 × 5 mL). The combined aqueous phases were neutralized with 4 M KOH solution and afterwards extracted with diethylether (3 × 10 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified via column chromatography (hexane/acetone 5:1) to yield a colorless solid (55.0 mg, 0.137 mmol, 37%).

R_f = 0.71 (hexane/acetone 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5 H, H_{Ar}), 7.08 (bs, 1 H, Pc-H_{Ar}), 6.51 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, Pc-H_{Ar}), 6.46 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, 1 H, Pc-H_{Ar}), 6.44 (d, $^3J_{HH}$ = 7.8 Hz, 1 H, Pc-H_{Ar}), 6.37 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.6 Hz, 1 H, Pc-H_{Ar}), 6.34 (d, $^4J_{HH}$ = 1.6 Hz, 1 H, Pc-H_{Ar}), 4.29 (d, $^2J_{HH}$ = 11.3 Hz, 1 H_2), 3.89 (d, $^2J_{HH}$ = 11.3 Hz, 1 H_2), 3.56 (q, $^3J_{HH}$ = 6.9 Hz, 1 HCH$_3$), 3.49–3.39 (m, 2 H, H_{Pc}), 3.25 (ddd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 7.3 Hz, 1 H, H_{Pc}), 3.10–3.03 (m, 2 H, H_{Pc}), 2.93–2.79 (m, 2 H, H_{Pc}), 2.71 (ddd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 3.5 Hz, 1 H, H_{Pc}), 2.32 (s, 6 H, N(CH_3)$_2$), 1.23 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7 (C$_{quart}$, C_{Ar}), 139.2 (C$_{quart}$, C_{Ar}), 138.7 (C$_{quart}$, C_{Ar}), 137.9 (C$_{quart}$, C_{Ar}), 137.5 (C$_{quart}$, C_{Ar}), 136.2 (C$_{quart}$, C_{Ar}), 135.3 (+, C_{Ar}H), 134.4 (+, C_{Ar}H), 131.1 (+, C_{Ar}H), 129.9 (+, C_{Ar}H), 129.7 (+, 2 × C_{Ar}H), 129.1 (+, C_{Ar}H), 128.9 (+, 2 × C_{Ar}H), 128.4 (+, C_{Ar}H), 128.2 (C$_{quart}$, C_{Ar}), 127.1 (+, C_{Ar}H), 61.9 (+, CHNMe$_2$), 42.5 (+, N(CH$_3$)$_2$), 37.2 (–, SCH$_2$), 34.5 (–, CH$_2$), 34.5 (–, CH$_2$), 34.1 (–, CH$_2$), 32.7 (–, CH$_2$), 14.5 (+, CHCH$_3$) ppm. IR (ATR) δ = 2927 (s), 2854 (m), 2777 (m), 1582 (w), 1494 (m), 1454 (m), 1369 (w), 1264 (w), 1156 (w), 1058 (m), 954 (w), 914 (m), 866 (m), 720 (m), 697 (m), 653 (m), 489 (w) cm^{-1}. MS (70 eV, EI), m/z (%): 401 (100) [M$^+$], 386 (51) [M$^+$ –CH$_3$], 356 (24) [M$^+$ –HNMe$_2$], 265 (20) [C$_{18}$H$_{17}$S$^+$], 175 (27) [C$_{12}$H$_{17}$N$^+$], 160 (27) [C$_{11}$H$_{14}$N$^+$], 131 (39) [C$_{10}$H$_{11}^+$]. HRMS (C$_{27}$H$_{31}$NS): calc. 401.2177, found 401.2174.

^{1}H NMR (400 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4d**:



^{13}C NMR (100 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4d**:

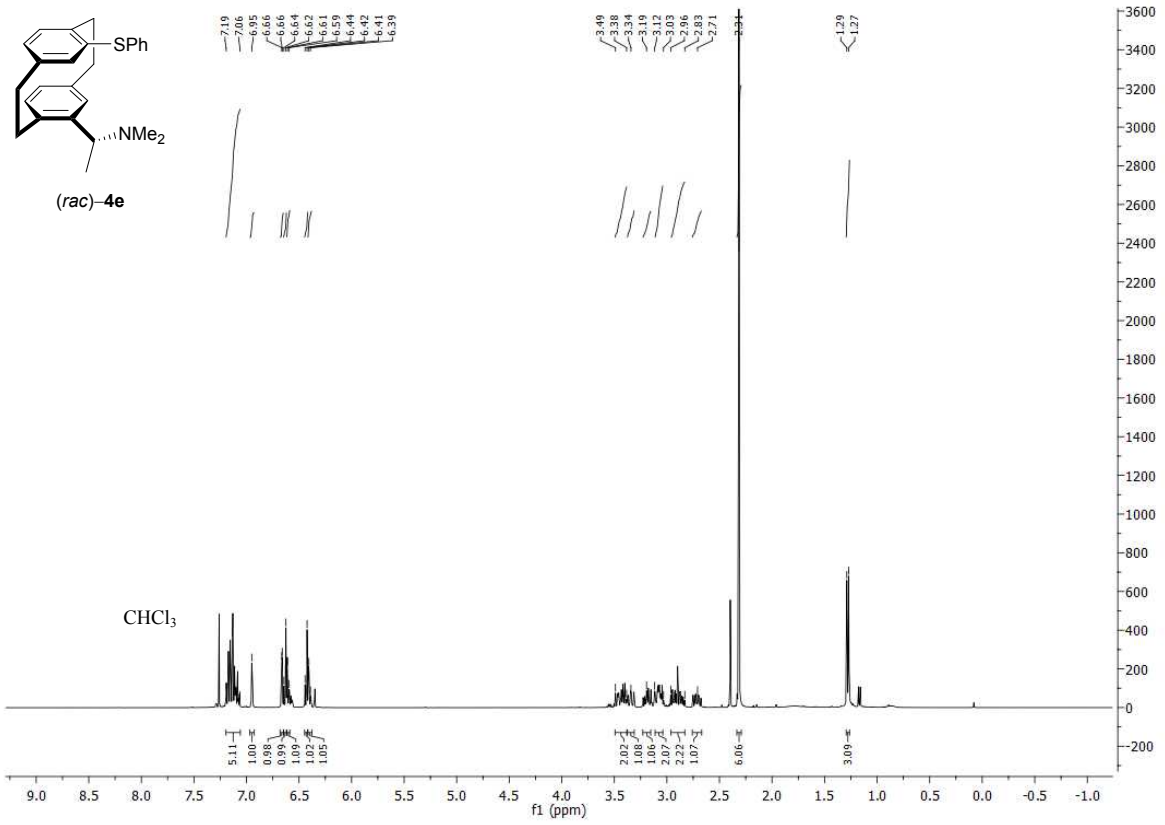


Synthesis of (R_p,*R*)/(S_p,*S*)-1-(4-phenylsulfanyl-[2.2]paracyclophane-16-yl-*N*,*N*-(dimethyl)ethylamine ((R_p,*R*)/(S_p,*S*)-**4e**):

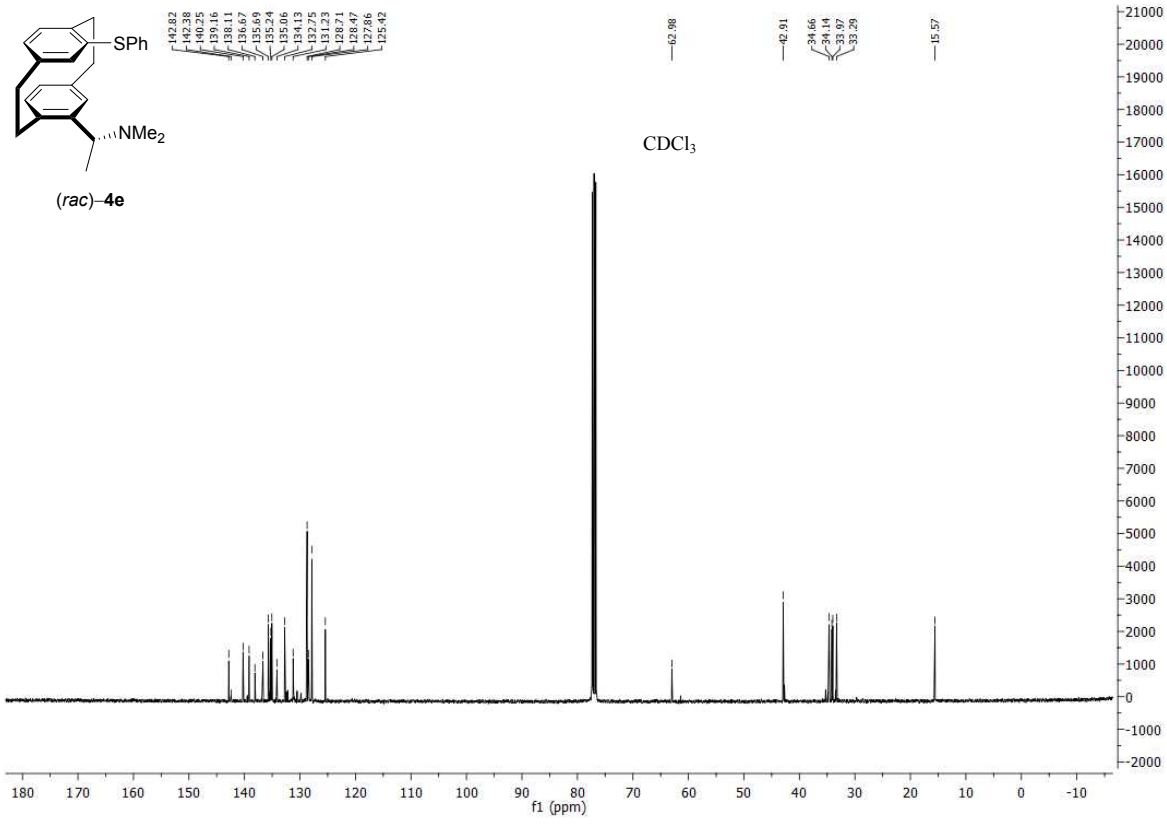
In a Schlenk flask, (R_p,*R*)/(S_p,*S*)-**2** (103 mg, 1.00 equiv., 0.369 mmol) was dissolved in 4 mL of dry cyclohexane. *s*BuLi (1.3 M in cyclohexane/hexane 92:8, 0.85 mL, 3.00 equiv., 1.11 mmol) was added and the solution was stirred for 24 h at 35 °C. Then, the mixture was diluted with 4 mL of dry hexane, cooled down to –78 °C and treated with dimethylformamide (328 mg, 4.05 equiv., 1.50 mmol). The reaction was allowed to warm up to room temperature within 5 hours and was stirred overnight. The following day, the mixture was diluted with 10 mL of diethylether, then washed with water (1 × 5 mL) and finally the organic phase was extracted with 1 M HCl (3 × 5 mL). The combined aqueous phases were neutralized with 4 M KOH solution and afterwards extracted with diethylether (3 × 10 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified via column chromatography (hexane/acetone 5:1) to yield a colorless solid (37.0 mg, 0.0959 mmol, 26%).

R_f = 0.73 (hexane/acetone 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.06 (m, 5 H, H_{Ar}), 6.95 (bs, 1 H, Pc-H_{Ar}), 6.66 (d, $^4J_{HH}$ = 1.6 Hz, 1 H, Pc-H_{Ar}), 6.63 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, Pc-H_{Ar}), 6.60 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, 1 H, Pc-H_{Ar}), 6.43 (d, $^3J_{HH}$ = 7.6 Hz, 1 H, Pc-H_{Ar}), 6.40 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.6 Hz, 1 H, Pc-H_{Ar}), 3.49–3.38 (m, 2 H_{Pc}, C*H*CH$_3$), 3.34 (ddd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 1.8 Hz, 1 H, H_{Pc}), 3.19 (ddd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 6.8 Hz, 1 H, H_{Pc}), 3.12–3.03 (m, 2 H, H_{Pc}), 2.96–2.83 (m, 2 H, H_{Pc}), 2.71 (ddd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 6.8 Hz, 1 H, H_{Pc}), 2.31 (s, 6 H, N(CH_3)$_2$), 1.28 (d, $^3J_{HH}$ = 7.0 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.8 (C_{quart}, C_{Ar}), 142.4 (C_{quart}, C_{Ar}), 140.3 (C_{quart}, C_{Ar}), 139.2 (C_{quart}, C_{Ar}), 138.1 (C_{quart}, C_{Ar}), 136.7 (C_{quart}, C_{Ar}), 135.7 (+, C_{Ar}H), 135.2 (+, C_{Ar}H), 135.1 (+, C_{Ar}H), 134.1 (C_{quart}, C_{Ar}), 132.8 (+, C_{Ar}H), 131.2 (+, C_{Ar}H), 128.7 (+, 2 × C_{Ar}H), 128.5 (+, C_{Ar}H), 127.9 (+, 2 × C_{Ar}H), 125.4 (+, C_{Ar}H), 63.0 (+, *C*HNMe$_2$), 42.9 (+, N(*C*H$_3$)$_2$), 34.7 (–, *C*H$_2$), 34.1 (–, *C*H$_2$), 34.0 (–, *C*H$_2$), 33.3 (–, *C*H$_2$), 15.6 (+, CH*C*H$_3$) ppm. IR (ATR) δ = 2929 (w), 1579 (w), 1475 (w), 746 (w) cm^{-1}. MS (70 eV, EI), m/z (%): 387 (92) [M$^+$], 372 (100) [M$^+$ –CH$_3$], 342 (31) [M$^+$ –HNMe$_2$], 211 (25) [$C_{14}H_{11}S^+$], 197 (15) [$C_{13}H_9S^+$], 175 (39) [$C_{12}H_{17}N^+$], 160 (35) [$C_{11}H_{14}N^+$], 131 (26) [$C_{10}H_{11}^+$]. HRMS ($C_{26}H_{29}NS$): calc. 387.2021, found 387.2023.

^{1}H NMR (400 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4e**:



^{13}C NMR (100 MHz, $CDCl_3$) of (R_p,*R*)/(S_p,*S*)-**4e**:

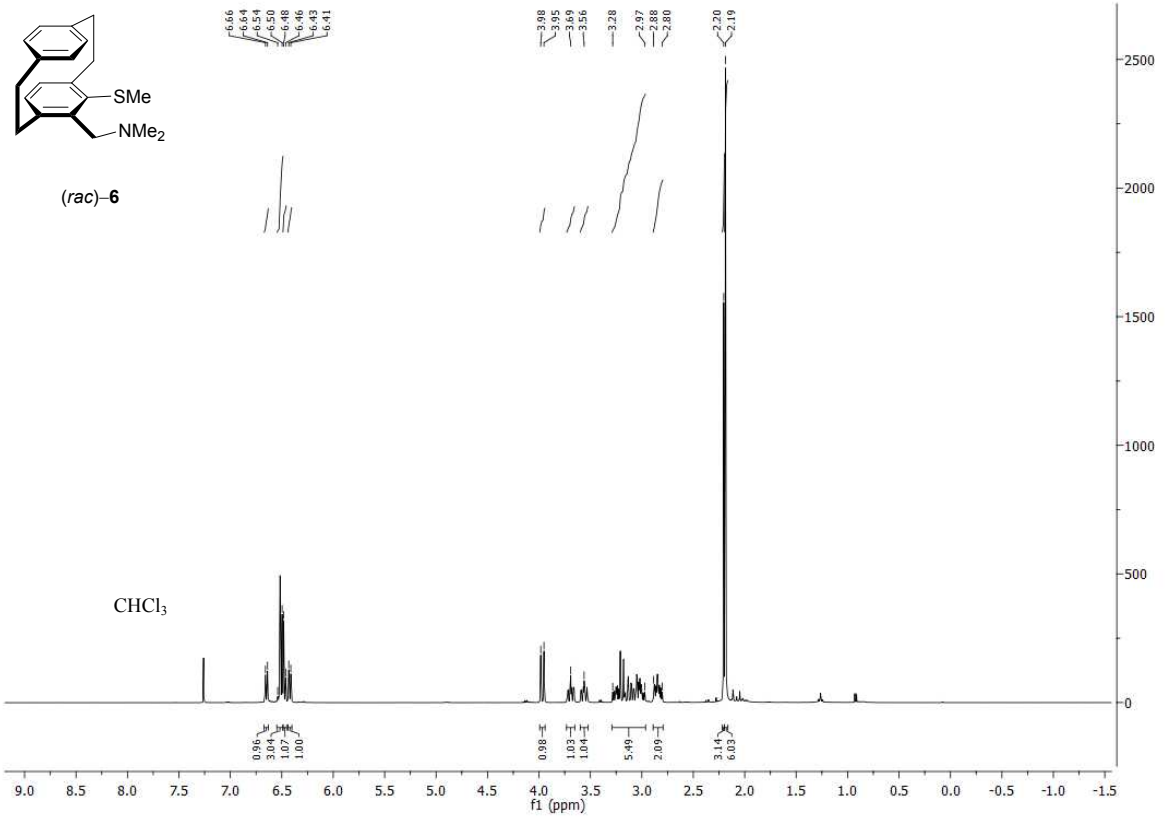


Synthesis of (*rac*)-5-*N,N*-dimethylaminomethyl-4-methylsulfanyl-[2.2]paracyclophane ((*rac*)-**6**):

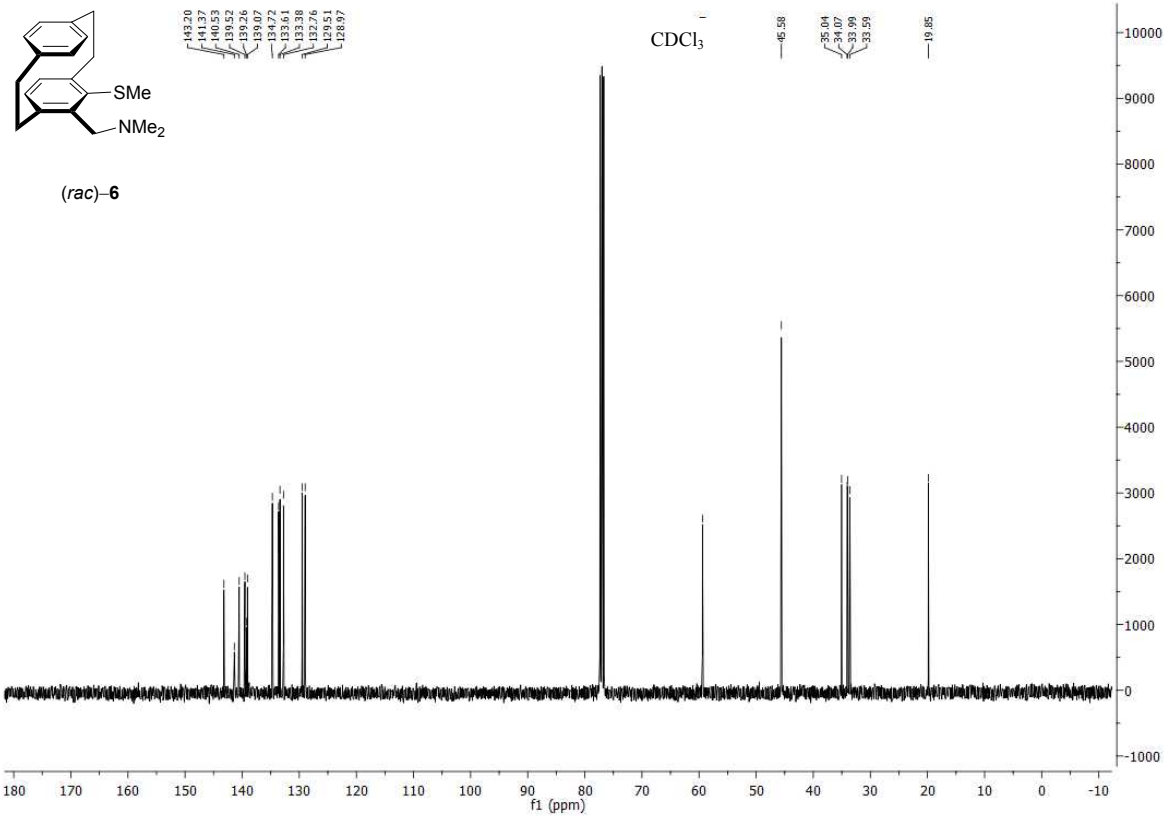
In a Schlenk flask, (*rac*)-**5** (260 mg, 1.00 equiv., 0.980 mmol) was dissolved in 10 mL of dry hexane. *s*BuLi (1.3 M in cyclohexane/hexane 92:8, 1.13 mL, 1.50 equiv., 1.47 mmol) was added and the solution was stirred for 3 hours at room temperature. Then, the mixture was cooled down to −78 °C and treated with dimethyl disulfide (196 µL, 2.26 equiv., 2.21 mmol). The reaction was allowed to warm up to room temperature within 5 hours and was stirred for further 2 hours. After addition of 10 mL water, the phases were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified via column chromatography (hexane/acetone 1:1) to yield a slightly yellow solid (80.0 mg, 0.255 mmol, 26%).

R_f = 0.27 (hexane/acetone 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (d, $^3J_{HH}$ = 8.0 Hz, 1 H, Pc-H_{Ar}), 6.54–6.50 (m, 3 H, Pc-H_{Ar}), 6.47 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, Pc-H_{Ar}), 6.42 (d, $^3J_{HH}$ = 8.0 Hz, 1 H, Pc-H_{Ar}), 3.97 (d, $^2J_{HH}$ = 12.5 Hz, 1 H, CH_2N), 3.69 (ddd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 2.7 Hz, 1 H, H_{Pc}), 3.56 (ddd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 2.2 Hz, 1 H, H_{Pc}), 3.28–2.97 (m, 5 CH_2N,H_{Pc}), 2.88–2.80 (m, 2 H_{Pc}), 2.20 (s, 3 H, SCH_3), 2.19 (s, 6 H, N(CH_3)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2 (C_{quart}, C_{Ar}), 141.4 (C_{quart}, C_{Ar}), 140.5 (C_{quart}, C_{Ar}), 139.5 (C_{quart}, C_{Ar}), 139.3 (C_{quart}, C_{Ar}), 139.1 (C_{quart}, C_{Ar}), 134.7 (+, C_{Ar}H), 133.6 (+, C_{Ar}H), 133.4 (+, C_{Ar}H), 132.8 (+, C_{Ar}H), 129.5 (+, C_{Ar}H), 129.0 (+, C_{Ar}H), 59.4 (–, CH$_2$N), 45.6 (+, N(CH$_3$)$_2$), 35.0 (–, CH$_2$), 34.1 (–, CH$_2$), 34.0 (–, CH$_2$), 33.6 (–, CH$_2$), 19.9 (+, SCH$_3$) ppm. IR (ATR) δ = 2920 (m), 2805 (w), 2759 (w), 1449 (w), 1169 (w), 1094 (w), 1024 (w), 940 (w), 852 (w), 796 (w), 718 (w), 520 (w) cm^{-1}. MS (70 eV, EI), m/z (%): 311 (100) [M^+], 296 (17) [M^+–CH_3], 251 (26) [M^+–$C_3H_{10}N$], 192 (60) [M^+–C_9H_{11}], 162 (21) [$C_9H_9NS^+$], 149 (16) [$C_9H_9S^+$], 104 (26) [$C_8H_8^+$]. HRMS ($C_{20}H_{25}NS$): calc. 311.1708, found 311.1705.

^{1}H NMR (400 MHz, $CDCl_3$) of (*rac*)-**6**:



^{13}C NMR (100 MHz, $CDCl_3$) of (*rac*)-**6**:

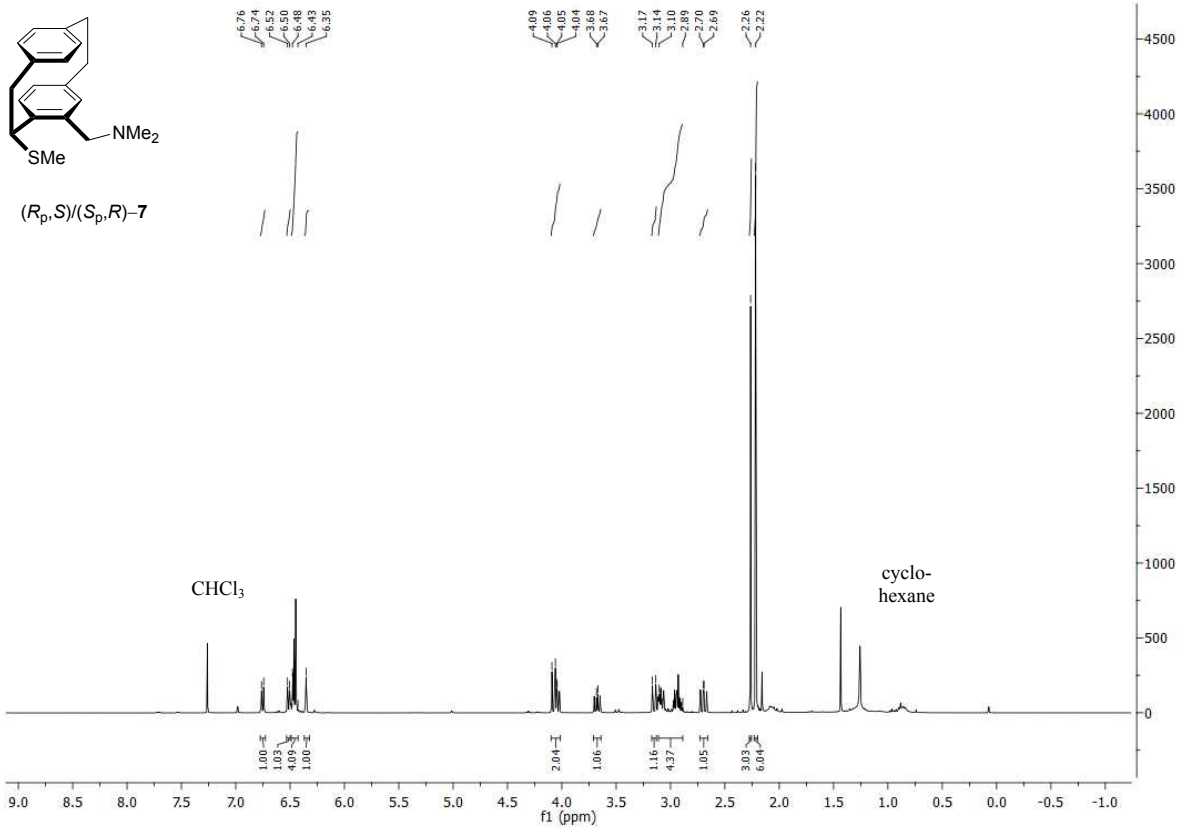


Synthesis of (R_p,*S*)/(S_p,*R*)-5-*N,N*-dimethylaminomethyl-4-methylsulfanyl-[2.2]paracyclophane ((R_p,*S*)/(S_p,*R*)-**7**):

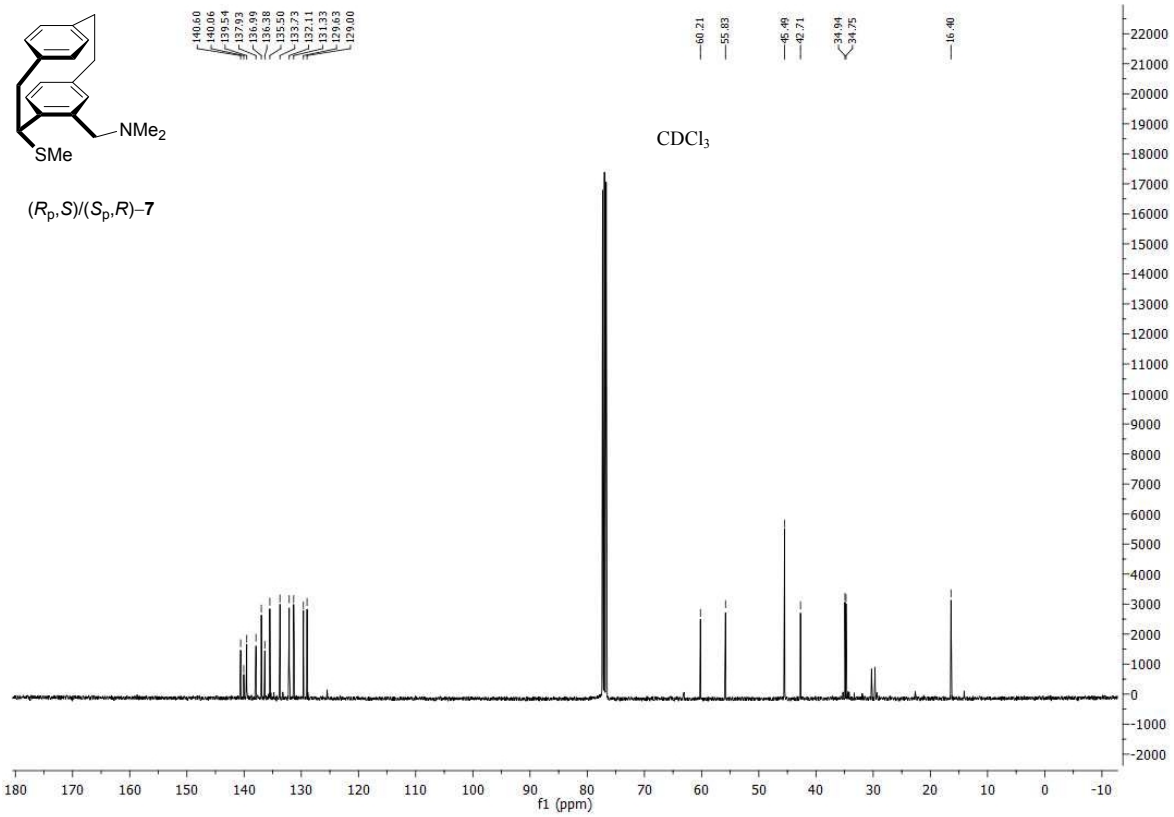
In a Schlenk flask, (*rac*)-**5** (260 mg, 1.00 equiv., 0.980 mmol) was dissolved in 10 mL of dry hexane. *s*BuLi (1.3 M in cyclohexane/hexane 92:8, 1.13 mL, 1.50 equiv., 1.47 mmol) was added and the solution was stirred for 3 hours at room temperature. Then, the mixture was cooled down to –78 °C and treated with dimethyl disulfide (196 µL, 2.26 equiv., 2.21 mmol). The reaction was allowed to warm up to room temperature within 5 hours and was stirred for further 2 hours. After addition of 10 mL water, the phases were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified via column chromatography (hexane/acetone 1:1) to yield a colorless solid (68.0 mg, 0.216 mmol, 22%).

R_f = 0.13 (hexane/acetone 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (d, $^3J_{HH}$ = 7.9 Hz, 1 H, Pc-H_{Ar}), 6.51 (d, $^3J_{HH}$ = 7.9 Hz, 1 H, Pc-H_{Ar}), 6.48–6.43 (m, 4 H, Pc-H_{Ar}), 6.35 (bs, 1 H, Pc-H_{Ar}), 4.08 (d, $^2J_{HH}$ = 12.6 Hz, 1 H, CH_2N), 4.04 (dd, $^2J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 8.4 Hz, 1 H, H_{Pc}), 3.67 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 8.3 Hz, 1 H, H_{Pc}), 3.15 (d, $^2J_{HH}$ = 12.5 Hz, 1 H, CH_2N), 3.10–2.98 (m, 4 H, H_{Pc}), 2.70 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 10.1 Hz, 1 H, H_{Pc}), 2.26 (s, 3 H, SCH_3), 2.22 (s, 6 H, N(CH_3)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6 (C_{quart}, C_{Ar}), 140.0 (C_{quart}, C_{Ar}), 139.5 (C_{quart}, C_{Ar}), 137.9 (C_{quart}, C_{Ar}), 137.0 (+, C_{Ar}H), 136.4 C_{quart}, C_{Ar}), 135.5 (+, C_{Ar}H), 133.7 (+, C_{Ar}H), 132.1 (+, C_{Ar}H), 131.3 (+, C_{Ar}H), 129.6 (+, C_{Ar}H), 129.0 (+, C_{Ar}H), 60.2 (–, CH$_2$N), 55.8 (+, CHS), 45.5 (+, N(CH$_3$)$_2$), 42.7 (–, CH$_2$CHS), 34.9 (–, CH$_2$), 34.8 (–, CH$_2$), 16.4 (+, SCH$_3$) ppm. IR (ATR) δ = 2927 (w), 1458 (w), 1027 (w), 718 (w), 540 (w) cm^{-1}. MS (70 eV, EI), m/z (%): 311 (100) [M$^+$], 296 (18) [M$^+$–CH$_3$], 253 (17) [$C_{17}H_{17}S^+$], 207 (20) [M$^+$–C_8H_8], 160 (99) [$C_{11}H_{14}N^+$], 149 (37) [$C_9H_9S^+$], 104 (12) [$C_8H_8^+$]. HRMS ($C_{20}H_{25}NS$): calc. 311.1708, found 311.1709.

^{1}H NMR (400 MHz, $CDCl_3$) of ((R_p,S)/(S_p,R)-**7**:



^{13}C NMR (100 MHz, $CDCl_3$) of ((R_p,S)/(S_p,R)-**7**:

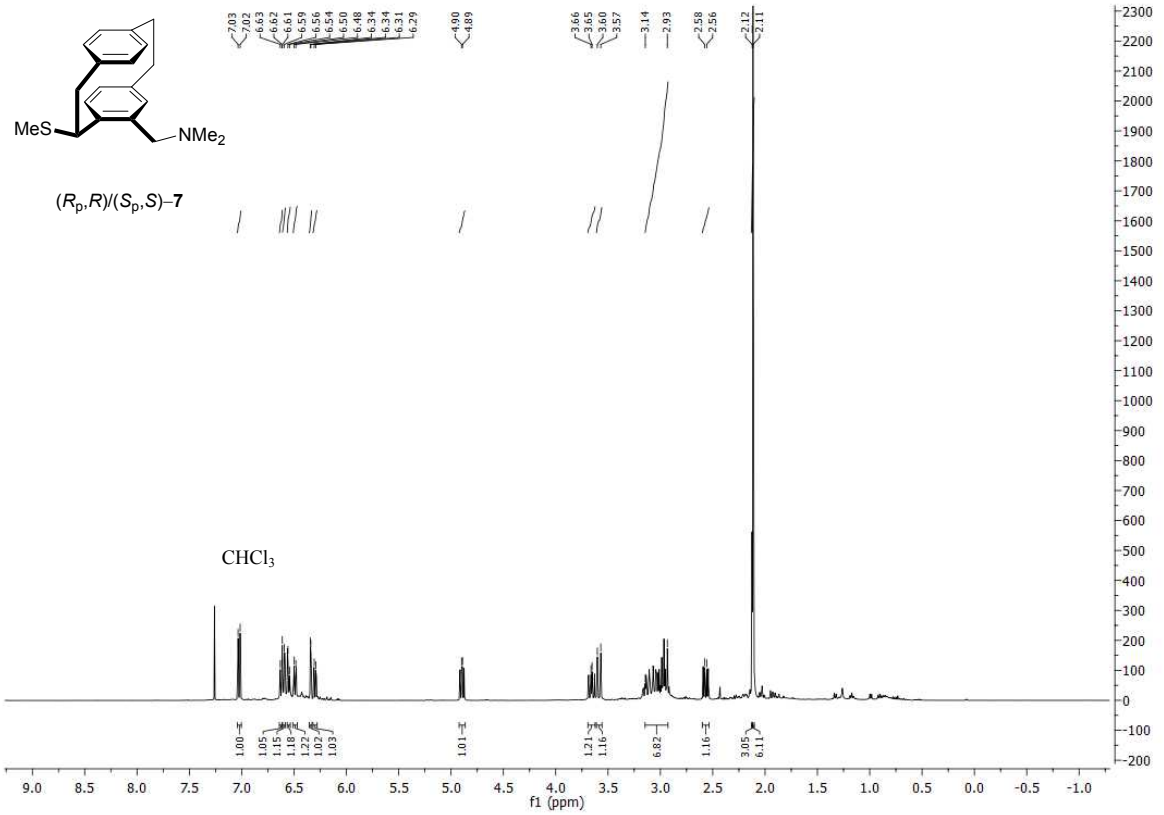


Synthesis of (R_p,*R*)/(S_p,*S*)-5-*N,N*-dimethylaminomethyl-4-methylsulfanyl-[2.2]paracyclophane ((R_p,*R*)/(S_p,*S*)-**7**):

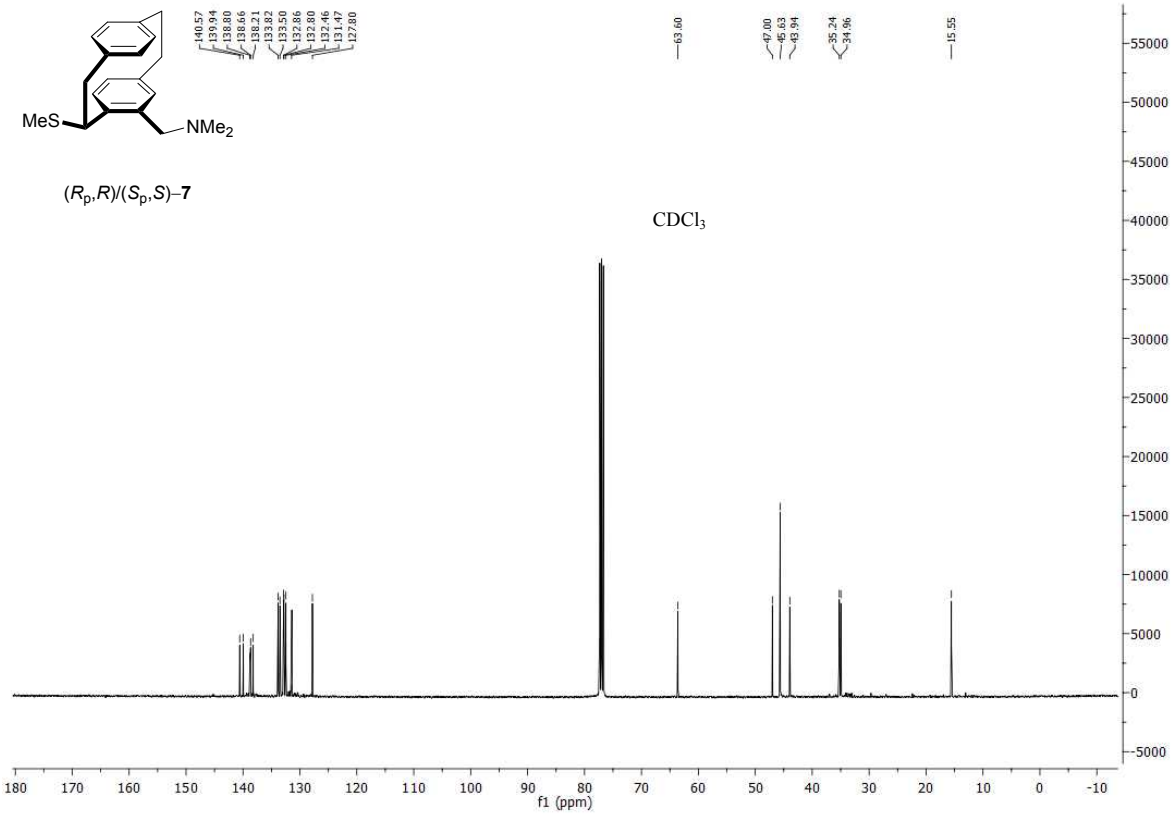
In a Schlenk flask, (*rac*)-**5** (260 mg, 1.00 equiv., 0.980 mmol) was dissolved in 10 mL of dry hexane. *s*BuLi (1.3 M in cyclohexane/hexane 92:8, 1.13 mL, 1.50 equiv., 1.47 mmol) was added and the solution was stirred for 3 hours at room temperature. Then, the mixture was cooled down to –78 °C and treated with dimethyl disulfide (196 µL, 2.26 equiv., 2.21 mmol). The reaction was allowed to warm up to room temperature within 5 hours and was stirred for further 2 hours. After addition of 10 mL water, the phases were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified via column chromatography (hexane/acetone 1:1) to yield a colorless solid (58.0 mg, 0.186 mmol, 19%).

R_f = 0.36 (hexane/acetone 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (d, $^3J_{HH}$ = 7.9 Hz, 1 H, Pc-H_{Ar}), 6.62 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.7 Hz, 1 H, Pc-H_{Ar}), 6.60 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.7 Hz, 1 H, Pc-H_{Ar}), 6.55 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.8 Hz, 1 H, Pc-H_{Ar}), 6.49 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.9 Hz, 1 H, Pc-H_{Ar}), 6.34 (d, $^4J_{HH}$ = 1.6 Hz, 1 H, Pc-H_{Ar}), 6.30 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.8 Hz, 1 H, Pc-H_{Ar}), 4.89 (dd, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 6.0 Hz, 1 H, H_{Pc}), 3.66 (dd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 9.6 Hz, 1 H, H_{Pc}), 3.59 (d, $^2J_{HH}$ = 13.1 Hz, 1 H, CH_2N), 3.14–2.93 (m, 6 H, 1 × CH_2N, 5 × H_{Pc}), 2.57 (dd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 6.0 Hz, 1 H, H_{Pc}), 2.12 (s, 3 H, SCH_3), 2.11 (s, 6 H, N(CH_3)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6 (C_{quart}, C_{Ar}), 140.0 (C_{quart}, C_{Ar}), 138.8 (C_{quart}, C_{Ar}), 138.7 (C_{quart}, C_{Ar}), 138.2 (C_{quart}, C_{Ar}), 133.8 (+, C_{Ar}H), 133.5 (+, C_{Ar}H), 132.9 (+, C_{Ar}H), 132.8 (+, C_{Ar}H), 132.5 (+, C_{Ar}H), 131.5 (+, C_{Ar}H), 127.8 (+, C_{Ar}H), 63.6 (–, CH$_2$N), 47.0 (+, CHS), 45.6 (+, N(CH$_3$)$_2$), 43.9 (–, CH$_2$CHS), 35.2 (–, CH$_2$), 35.0 (–, CH$_2$), 15.6 (+, SCH$_3$) ppm. IR (ATR) δ = 2933 (w), 1436 (w), 1030 (w), 716 (w), 536 (w) cm^{-1}. MS (70 eV, EI), m/z (%): 311 (100) [M^+], 296 (17) [M^+–CH_3], 251 (54) [M^+–$C_3H_{10}N$], 160 (83) [$C_{11}H_{14}N^+$], 145 (45) [$C_{10}H_{10}N^+$], 104 (21) [$C_8H_8^+$]. HRMS ($C_{20}H_{25}NS$): calc. 311.1708, found 311.1704.

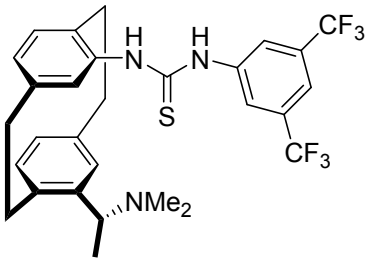
^{1}H NMR (400 MHz, $CDCl_3$) of ((R_p,R)/(S_p,S)-**7**:



^{13}C NMR (100 MHz, $CDCl_3$) of ((R_p,R)/(S_p,S)-**7**:



Synthesis of (R_p,*R*)/(S_p,*S*)-*N*-1-(3,5-bis(trifluoromethyl)phenyl)-4-*N*'-([2.2]paracyclophane-16-yl-*N*,*N*-(dimethyl)ethylamino)thiourea



In a Schlenk flask, (*rac*)-**4b** (25.0 mg, 1.00 equiv., 78.0 µmol) was dissolved in 10 mL of dry diethylether and treated with lithium aluminum hydride (12.0 mg, 4.10 equiv., 0.320 mmol) at 0 °C. The reaction was allowed to warm up to room temperature and was stirred for further 20 hours. The mixture was neutralized by addition of saturated, aqueous ammonia hydrochloride solution. The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was solved in 5 mL of dichloromethane and bis(trifluoromethyl)isothiocyanate (29.0 µL, 2.05 equiv., 0.160 mmol) was added. The mixture was stirred for 16 hours. Afterwards, the solvent was evaporated under reduced pressure. The crude product was purified via column chromatography (hexane/acetone 5:1) to yield a yellowish oil (20.0 mg, 35.1 µmol, 45%).

R_f = 0.44 (hexane/acetone 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.92 (s, 1 H, N*H*), 8.02 (s, 1 H, H_{Ar}), 7.64 (s, 1 H, H_{Ar}), 7.62 (s, 1 H, H_{Ar}), 7.00 (bs, 1 H, Pc-H_{Ar}), 6.62 (d, $^3J_{HH}$ = 8.0 Hz, 1 H, Pc-H_{Ar}), 6.55 (dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.9 Hz, 1 H, Pc-H_{Ar}), 6.54 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, Pc-H_{Ar}), 6.44 (dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, 1 H, Pc-H_{Ar}), 6.33 (bs, 1 H, Pc-H_{Ar}), 3.66 (q, $^3J_{HH}$ = 6.9 Hz, 1 H, C*H*CH$_3$), 3.34–2.80 (m, 8 H, H_{Pc}), 2.69 (s, 6 H, N(CH_3)$_2$), 1.16 (d, $^3J_{HH}$ = 6.9 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (C_{quart}, *C*S), 145.0 (C_{quart}), 142.7 (C_{quart}), 140.2 (C_{quart}), 140.0 (C_{quart}), 136.6 (C_{quart}), 136.5 (C_{quart}), 135.9 (+, C_{Ar}H), 135.5 (C_{quart}), 134.2 (+, C_{Ar}H), 133.6 (+, C_{Ar}H), 131.9 (C_{quart}), 131.6 (+, C_{Ar}H), 127.5 (+, C_{Ar}H), 126.0 (+, C_{Ar}H), 125.8 (C_{quart}), 124.3 (+, C_{Ar}H), 121.7 (C_{quart}), 118.8 (+, C_{Ar}H), 61.3 (+, *C*HCH$_3$), 42.0 (+, N(*C*H$_3$)$_2$), 34.8 (–, *C*H$_2$), 34.0 (–, *C*H$_2$), 31.6 (–, *C*H$_2$), 29.7 (–, *C*H$_2$), 13.6 (+, CH*C*H$_3$) ppm. IR (ATR) δ = 2929 (w), 1472 (w), 1379 (w), 1278 (w), 885 (w), 681 (w) cm^{-1}. MS (70 eV, EI), m/z (%): 565 (12) [M^+], 294 (29) [M^+–$C_9H_3F_6NS$], 271 (100) [$C_9H_3F_6NS^+$], 229 (48) [$C_8H_5F_6N^+$], 131 (26) [$C_9H_9N^+$]. HRMS ($C_{29}H_{29}F_6N_3S$): calc. 565.1986, found 565.1985.

2. DFT CALCULATIONS

The geometries of all considered symmetric dimers (homo and homo-meso dimers) were optimized using density functional theory (DFT) methods as implemented in the TURBOMOLE program [1]. We used the TPSS [2] functional either in combination with a def2-SVP basis set (TPSS/SVP) or in combination with a larger def2-TZVP basis set and an additional correction to account for dispersion interactions [3] (TPSS-D3/TZVP). All calculations were performed using the efficient resolution of the identity (RI) approximation for the evaluation of four-center Coulomb integrals. Tight convergence criteria (SCF energy: 10^{-8} E_h, gradient: 10^{-4} E_h/a_0 and inclusion of the derivatives of quadrature weights) and an integration grid of m4 quality were employed. The optimized homo dimer structures exhibit C_2 symmetry while the homo-meso structures have C_i symmetry (except for isomer 1, which is C_1 symmetric). All optimized structures were confirmed to be minima on the potential energy surface by calculation of the harmonic vibrational frequencies.

Table 1. Relative energies of the various lithio (*R*,R_P**)-**2** dimers in kJ/mol.

	TPSS/SVP		TPSS-D3/TZVP	
Isomer	homo	homo-meso	homo	homo-meso
1	38.8	40.7	45.9	48.5
2	115.0	113.9	130.3	133.6
3	114.2	112.1	145.6	143.8
4	99.1	98.2	126.9	126.9
5	98.6	97.1	127.9	127.5
6	26.4	25.9	37.3	39.2
7	34.3	35.3	45.0	45.1
8	0.0	11.9	0.0	15.1

9	116.3	113.4	146.2	146.7
10	120.3	117.5	148.0	145.6
11	96.0	95.3	119.4	119.8
12	94.1	92.6	116.5	116.8
13	114.6	111.6	143.6	140.9
14	52.1	53.4	42.8	51.8
15	8.6	8.7	9.1	9.6

Table 2. Relative energies of the various lithio (*rac*)-**5** dimers in kJ/mol.

	TPSS/SVP		TPSS-D3/TZVP	
Isomer	homo	homo-meso	homo	homo-meso
1	14.2	17.4	10.1	13.0
2	108.5	108.9	108.1	120.6
3	104.4	102.4	125.0	123.4
4	86.3	85.1	101.4	101.0
5	90.9	89.6	107.0	106.0
6	3.1	2.3	6.6	7.0
7	0.0	2.8	3.8	8.2
8	16.9	25.5	0.0	11.6
9	106.4	104.2	126.7	124.4
10	107.3	104.4	123.8	121.3

11	87.1	86.0	98.8	98.7
12	86.2	84.8	96.8	97.7
13	100.7	98.5	116.4	114.5
14	55.5	58.6	31.3	42.0
15	18.2	18.6	3.6	3.6

3. CRYSTALLOGRAPHY

3.1. Crystal Structure Determinations

All single-crystal X-ray diffraction studies were carried out on a Bruker-Nonius Kappa-CCD diffractometer at 123(2) K (using MoKα radiation (λ = 0.71073 Å). Direct Methods (SHELXS-97 [4]) were used for structure solution and refinement was carried out using SHELXL-97 [4] (full-matrix least-squares on F^2). Hydrogen atoms were localized by difference electron density determination and refined using a riding model. The absolute configuration of **2** could not be determined reliably be refinement of Flack's x-parameter (x = 0(3)) [5] nor Hofft's y-parameter (y = 0.7(6)). [6] In **4e** the dimethylamine group is disordered.

Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1035385 (**2**), CCDC-1035386 (**4e**), CCDC-1035387 (**6**), and CCDC-1035388 (**7**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: int.code+(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).

2: colourless crystals, $C_{20}H_{25}N$, M = 279.41, crystal size 0.40 x 0.25 x 0.15 mm, T = 123(2) K, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 10.529(1) Å, b = 11.655(1) Å, c = 12.596(1) Å, V = 1545.7(2) Å^3, Z = 4, ρ(calc) = 1.201 Mg m^{-3}, F(000) = 608, μ = 0.069 mm^{-1}, 37108 reflections ($2\theta_{max}$ = 55°), 3519 unique [R_{int} = 0.030], 192 parameters, $R1$ (for 3333 $I > 2\sigma(I)$) = 0.035, *wR2 (all data)* = 0.089, S = 1.05, largest diff. peak and hole 0.233 and -0.151 e Å^{-3}, x = 0(3).

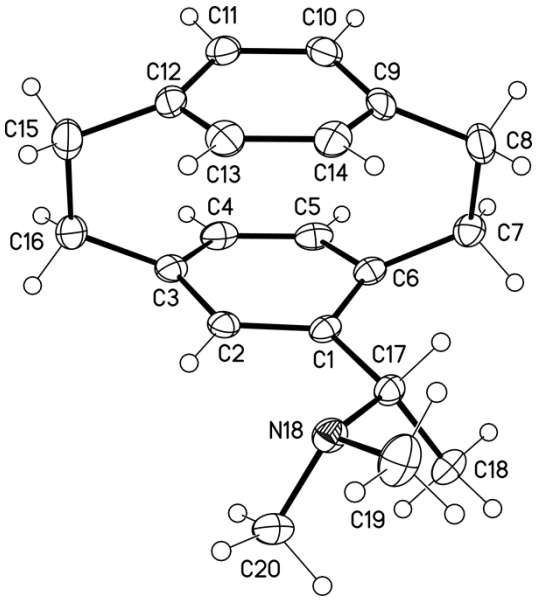


Fig. Xray-S1. Molecular structure of **2** (displacement parameters are drawn at 50% probability level).

4e: colourless crystals, $C_{26}H_{29}NS$, M = 387.56, crystal size 0.40 x 0.35 x 0.30 mm, T = 123(2) K, monoclinic, space group $P2_1/c$ (No. 14), a = 7.535(1) Å, b = 14.973(2) Å, c = 18.844(2) Å, β = 95.77(1)°, V = 2115.2(2) Å^3, Z = 4, ρ(calc) = 1.217 Mg m^{-3}, F(000) = 832, μ = 0.164 mm^{-1}, 38450 reflections ($2\theta_{max}$ = 55°), 4847 unique [R_{int} = 0.036], 252 parameters, 43 restraints, $R1$ (for 3955 $I > 2\sigma(I)$) = 0.051, *wR2 (all data)* = 0.126, S = 1.06, largest diff. peak and hole 0.523 and -0.471 e Å^{-3}.

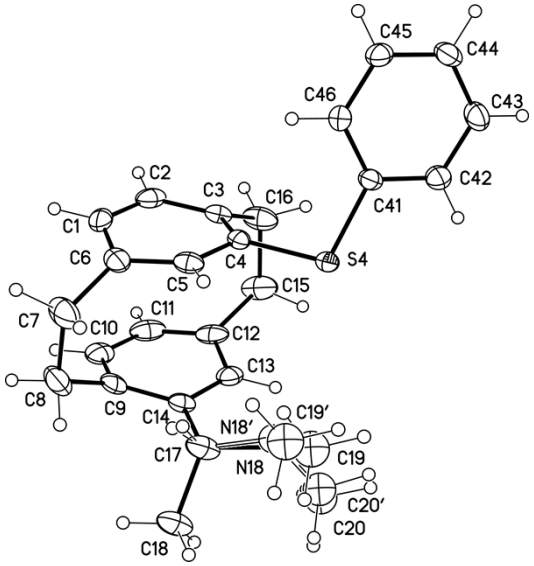


Fig. Xray-S2. Molecular structure of **4e** (displacement parameters are drawn at 50% probability level).

6: colourless crystals, $C_{20}H_{25}NS$, M = 311.47, crystal size 0.30 x 0.20 x 0.15 mm, T = 123(2) K, monoclinic, space group $P2_1/n$ (No. 14), a = 8.104(1) Å, b = 8.358(1) Å, c = 24.688(3) Å, β = 96.20(1)°, V = 1662.4(3) Å^3, Z = 4, ρ(calc) = 1.244 Mg m^{-3}, F(000) = 672, μ = 0.192 mm^{-1},19143 reflections ($2\theta_{max}$ = 55°), 3803 unique [R_{int} = 0.040], 202 parameters, $R1$ (for 3114 $I > 2\sigma(I)$) = 0.044, *wR2 (all data)* = 0.107, S = 1.06, largest diff. peak and hole 0.347 and -0.318 e Å^{-3}.

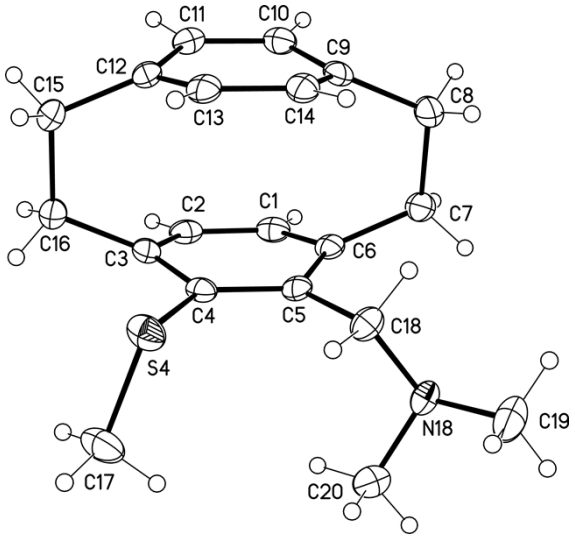


Fig. Xray-S3. Molecular structure of **6** (displacement parameters are drawn at 50% probability level).

7: colourless crystals, $C_{20}H_{25}NS$, M = 311.47, crystal size 0.50 x 0.30 x 0.10 mm, T = 123(2) K, monoclinic, space group $P2_1/c$ (No. 14), a = 7.812(1) Å, b = 11.736(1) Å, c = 18.668(2) Å, β = 96.49(1)°, V = 1700.5(3) Å^3, Z = 4, ρ(calc) = 1.217 Mg m^{-3}, F(000) = 672, μ = 0.188 mm^{-1}, 13865 reflections ($2\theta_{max}$ = 55°), 3870 unique [R_{int} = 0.039], 202 parameters, $R1$ (for 2923 $I > 2\sigma(I)$) = 0.046, *wR2 (all data)* = 0.111, S = 1.03, largest diff. peak and hole 0.274 and -0.262 e Å^{-3}.

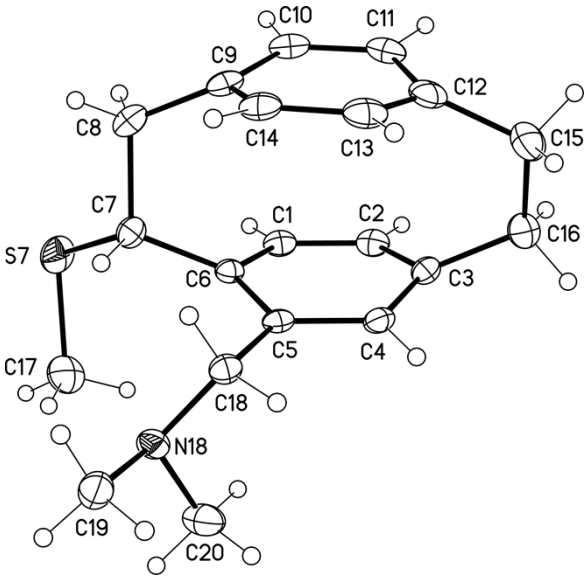


Fig. Xray-S4. Molecular structure of **7** (displacement parameters are drawn at 50% probability level).

4. References and Notes

[1] TURBOMOLE V6.6 2014, a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989–2007, TURBOMOLE GmbH, since 2007; available from http://www.turbomole.com.

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