Enantiomerically Pure [2.2]Paracyclophane–4–thiol: A Planar Chiral Sulfur-based Building Block Readily Available by Resolution with an Amino Acid Chiral Auxiliary

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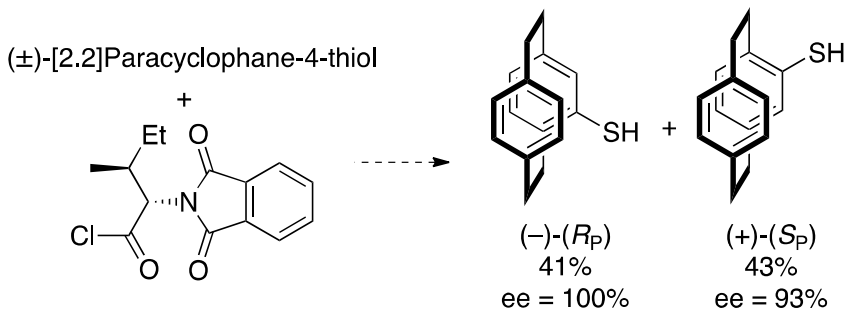
Graphical Abstract



Abstract: Acyl chloride of *N*-phthaloyl-(*S*)-isoleucine is an efficient chiral auxiliary for the resolution of (±)-[2.2]paracyclophane-4-thiol. A preparative protocol,based on theconversion into diastereoisomeric thiolesters andseparation by two fractional crystallizations and column chromatography, was developed. Deprotection with $LiAlH_4$ allowed isolation of the individual thiol enantiomers in good yield (~ 40%) and high enantiomeric purity (ee > 93%). The absolute configurations were determined by comparison of the optical rotation value of the products with literature data, and confirmed by X-ray crystallography.

[2.2]Paracyclophane (PCP) **1**(R^1 = H) is the parent hydrocarbon for a fascinating family of organic compounds consisting of a rigid cofacial arrangement of two benzene unitsbridged at the *para* positions by CH_2CH_2 groups (Figure 1).[1]Following the pioneering reports by Brown, Farthing and Crammore than sixty years ago,[2]the appealing structural, physical and electronic properties of [2.2]PCP derivatives haveresulted in significant attention.[3] They have been applied successfully in numerous fields, such as polymer science,[4]advanced materials,[5]medicinal chemistry[6] and catalysis[7].

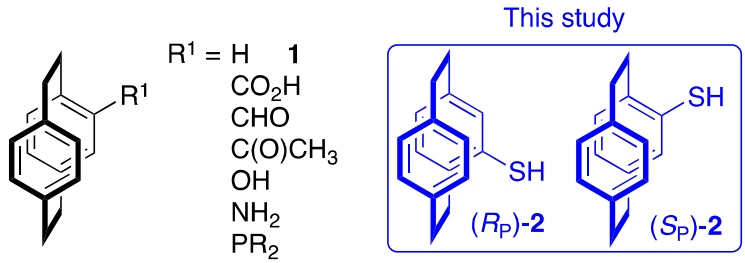


Figure 1. [2.2]Paracyclophane **1** and monosubstituted derivatives.

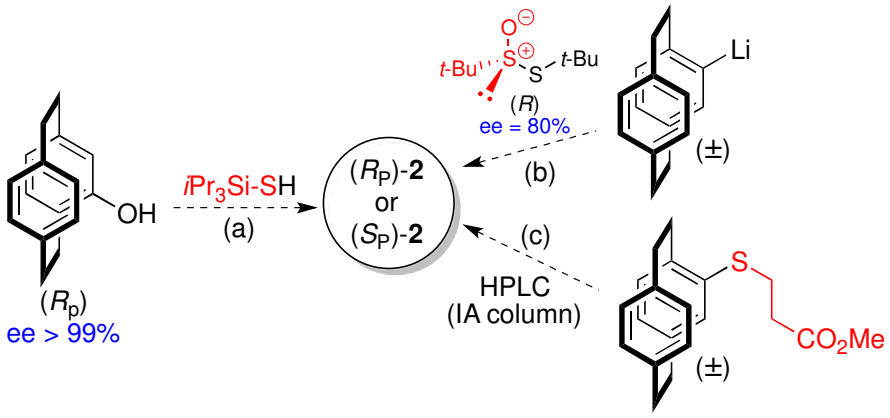
Stereochemistry is an important facet of [2.2]PCP compounds resulting from the inherent planar chirality of these systems. Unlike other classical planar chiral frameworks such as ferrocenes or η^6-arene transition-metal complexes, that require two substituents on an aromatic ring to become chiral, the presence of a single substituenton the [2.2]PCP skeletonis enough to break the plane of symmetry of the molecule and hence to generate chirality.

Access to enantiopure [2.2]PCP derivatives is however not straightforward.[8]The commercial availability of non racemic [2.2]PCPs remains extremely limited, with the additional restriction of prohibitive cost. No asymmetric synthesis is available from the much cheaper achiral hydrocarbon **1**, derivatization of which inevitablyfurnishes a racemic mixture. Hence approaches to enantiopure [2.2]PCPsrely on protocols for the resolution of racemates. Conventional strategies[9] are based on i) conversion into a pair of diastereoisomers by reaction with a chiral auxiliary, followed by separation using column chromatography, or better, fractional crystallization, and ii) the enantioseparation on preparative HPLC with a chiral stationary phase.[10] These resolution techniques can be conductedon the final target, or earlier on a precursor.As a consequence, further increasesinthe potential of planar chiral [2.2]PCPs is directly related tothe availability by resolutionof a pool of simple chiral [2.2]PCP-based building blocks. In this context, most privileged monosubstituted scaffolds possess a carbonyl[11a-c][R^1 = CO_2H, CHO, $C(O)CH_3$] function, a hydroxyl[11d] (R^1 = OH),an amino[11e](R^1 = NH_2) or a diphosphino group[11f-g](R^1 = PR_2)(Figure 1).

In retrospect, the case of a sulfur substituenthas been particularly neglected. This paucity of literature is most likely due to the difficulties faced for the introduction of the heteroatom on the [2.2]PCP core.[12] Given the wide reactivity of the sulfanyl group,[13] [2.2]paracyclophane-4-thiol **2**(R^1 = SH) can rapidly be identified as a suitable chiral sulfur-based candidate (Figure 1). Access to a single enantiomerof(R_P)-**2** or *(S_P)*-**2** has been restricted toonly three studies (Scheme 1).[14] Bräse used as starting material (*R*)-[2.2]paracyclophan-4-ol (ee > 99%), previously obtained by enzymatic resolution of the racemic acetoxy analogue with *Candida cyclindracea* lipase.[14a]The sulfur atom was then introduced by a palladium cross-coupling reaction of the corresponding triflate with triisopropylsilanethiol(route a). Rowlands took profit from the Andersen approach and employed enantioenriched (*R*)-*tert*-butyl *tert*-butanethiosulfinate (ee = 80%, Ellman

thiosulfinate) as both sulfur source and chiral auxiliary.[14b] Reaction with (±)-4-lithio[2.2]paracyclophane furnished a 1:1 mixture of the two diastereoisomersof 4-*tert*-butylsulfinyl-[2.2]paracyclophane, which were easily separatedon a silica gel column (route b). More recently, our group described the separation of a racemic [2.2]PCP-based sulfanyl ester by semi-preparative high performance liquid chromatography (HPLC) with a chiral stationary phase (IA column, route c).[14c] Even if satisfactory enantiomeric excesses were reached,[15] limitations can however be pointed out, such as the use of specialized tools and/or equipment (enzyme, semipreparative HPLC with specific columns), ora low chemical yields for the final functional manipulations to deliver the free S–H group[16]. Therefore, the development of an alternative resolution approach to furnish enantiopure thiol (R_P)-**2** or (S_P)-**2**is still highly desirable.Attractive features to fulfill would ideally include the use of a cheap enantiopure chiral auxiliary, if possible available from the chiral pool, a simple procedure amenable to scale up, and a short and efficient deprotection step.

Scheme 1. Previous Approaches to a Single Enantiomer of Thiol 2



On this basis, and following our ongoing interest in [2.2]PCP chemistry,[17] we decided to address this challenge and focused on an approach mediated by a chiral auxiliary. We present herein the results of our investigation, which led to the development of a resolution procedure of (±)-**2**perfectly fulfilling the aforementioned criteria.

Having previously described a straightforward and high-yielding method to access racemic thiol (±)-**2**, [18] we decided to focus on the direct resolution of this compound.Enantiopure chiral auxiliaries**3a-g**, displaying contrasting structural features, were screened (Figure 2). Derivatives of (–)-menthol, (–)-camphanic acid, (+)-naproxen and *L*-amino acids were investigated.[19]These exploratory studies were performed starting with50 mg of (±)-**2**(0.21 mmol scale). The chiral fragments were attached to (±)-**2**by *C*–*S*covalent bonding, *via* the corresponding chloroformate **3a** or acid chlorides **3b-g**. The desired diastereoisomeric *S*-acyl compounds **4a-g** were isolated, without optimization of the protocol, with yields ranging from 44 to 100%.

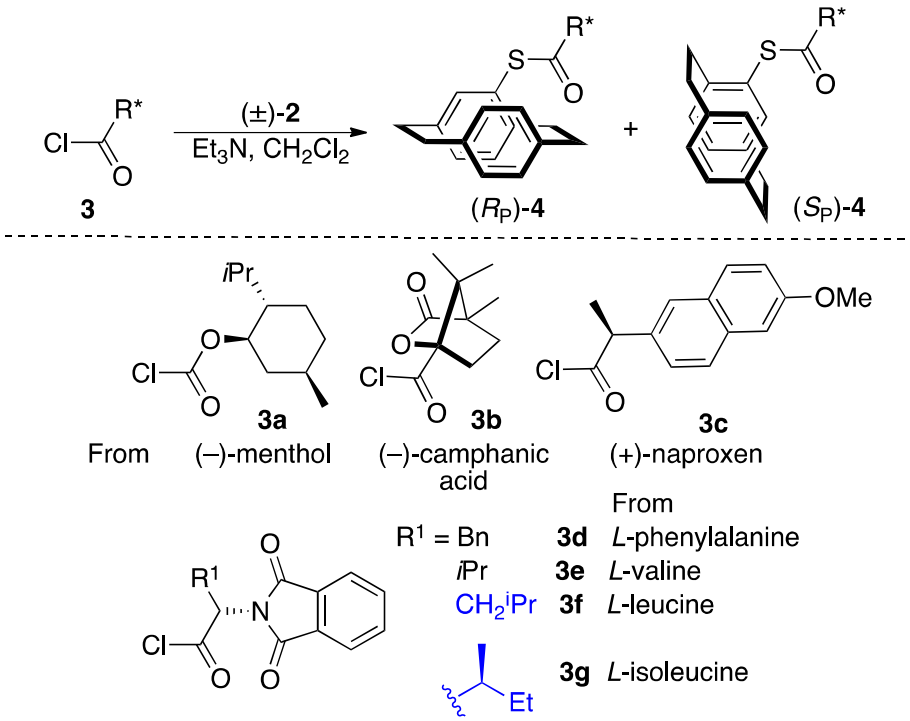


Figure 2. Chiral auxiliaries **3**tested for the resolutionof (±)-**2**.

For chiral auxiliaries **3a-e**, our efforts failed to find an eluent system, which would allow a practical level of separation of both epimers of **4a-e** by chromatography on silica gel. In contrast, a more favorable case was observed with**4f** derived from *L*-leucine.[20] Despite a tedious separation at the preparative scale,[21] it was possible to collect fractions containing only the fast-eluting diastereoisomer of **4f**.[22] Removal of the chiral auxiliary by reductionwith

$LiAlH_4$furnished thiol (–)-**2**in 96% yield andwithperfect enantiopurity, according to HPLC[23]chromatograph. Much to our delight, single crystals ofthe diastereopure thiolester**4f**, and also the corresponding enantiopure thiol (–)-**2**,[24]were suitable for X-ray analysis (Figure 3). They enabled a consistentassignment of configuration, withrespectively a(R_P,*S*) stereochemistryfor the isolated diastereoisomer of**4f**, and a (R_P) configurationfor (–)-**2**(Flack parameter =0.03).This conclusionis also in perfect agreement with the specific rotation value of thiol (R_P)-**2**determined as($[\alpha]_D^{20}$–219.8**)**.[25]

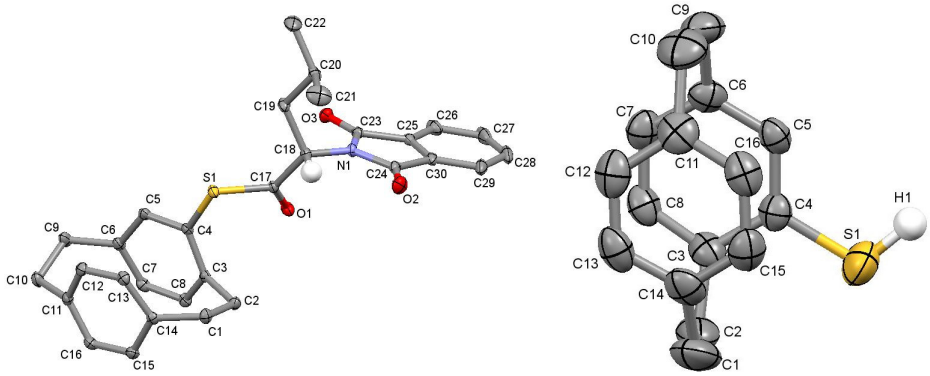
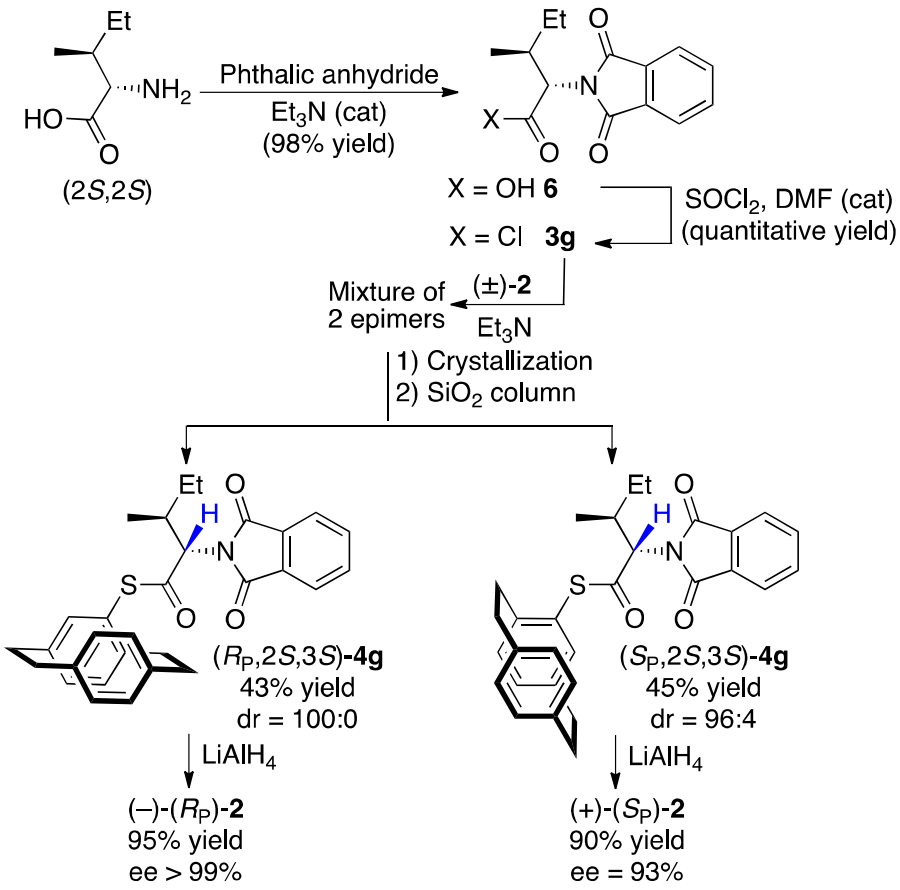


Figure 3. ORTEP diagrams of (R_P,*S*)-**4f**(left) and (R_P)-**2**(right) with ellipsoids shown at the 50% probability level. All hydrogen atoms have been omitted, except important ones.

Theresolution was even better when*L*-isoleucine was used. The results are presented hereafter in full detail (Scheme 2). The synthesis of chiral auxiliary **3g** started with protection of the primary amine of *L*-isoleucinewith phthalic anhydride, to furnish phthalimide derivative **6** in 98% yield. Subsequent reaction in the presence of $SO_2Cl_2$and a catalytic amount of DMF, allowed activation of the carboxylic acid with the formation of the acid chloride **3g**(quantitative yield). The sequence is operationally simple, and the product is obtained without the need for purification steps.

Scheme 2. Resolution of (±)-2 with3g Derived from *L*-Isoleucine



Racemic [2.2]paracyclophane-4-thiol (±)-**2** and freshly prepared acid chloride **5** were then reacted at room temperature, in dichloromethane,in the presence oftriethylamine. The mass balance and analysis of the ^{1}H NMR spectrum of the crude product indicated full conversion into the thiolester **4g**. The two diastereoisomers are produced as expected in equimolecular amounts.[26] The doublets for the proton *alpha* to the carbonyl group, and attached to the same carbon as the phthalimide group (labeled in blue in Scheme 2),are well separated from the rest of the signals and were laterused as probes to estimate the diastereoisomeric ratio. Notably, during preliminary tests to identify the appropriate solvent combination for separation of the diastereoisomers of **4g** on silica gel, a dramatic difference in the solubility of both compounds in n-heptane/$CHCl_3$ mixtures was observed. Precipitation of the less soluble isomer was even noticed with certainsolvent ratios. This was exploited to develop an easy-to-use resolution process, in which a substantial amount of one diastereoisomerresulted from fractional crystallization. The simple protocol we have

developed was optimizedfor 500 mg of thiol (±)-**2** (2.1 mmol scale). The purity of each fraction was verified by ^{1}H NMR analysis.

A fractional crystallization was first carried out in 10 mL of a 4:1 *n*-heptane/$CHCl_3$ mixture and led to the isolation of 295 mg of (R_P,2*S*,3*S*)-**4g**. Subsequent crystallization of the mother liquors, in 4 mL of the same solvent system, was then performed and allowed the isolation of an additional 80 mg of (R_P,2*S*,3*S*)-**4g**. Finally, purification of the supernatant by column chromatography on silica gel with a 4:1 *n*-pentane/Et_2O mixture as eluent enabled the collection of an additional 53 mg of diastereoisomer (R_P,2*S*,3*S*)-**4g** (Rf of 0.26) in addition to 475 mg of diastereoisomer (S_P,2*S*,3*S*)-**4g** (Rf of 0.23). All fractions of (R_P,2*S*,3*S*)-**4g** were diastereopure. Diastereoisomer (S_P,2*S*,3*S*)-**4g** isolated after column chromatography was contaminated by only 4% of (R_P,2*S*,3*S*)-**4g**. In summary, this overall resolution protocol, combining two crystallizations and a chromatographic separation, led to the isolation of 428 mg of (R_P,2*S*,3*S*)-**4g** (43% yield, dr = 100:0), whilst diastereoisomer (S_P,2*S*,3*S*)-**4g** was obtained in 45% yield (475 mg, dr = 96:4). Despite many attempts, we did not succeed in growing suitable crystals of either diastereoisomer, which would have allowed the immediate determination of the absolute stereochemistry of the products.

Removal of the chiral auxiliary was then conveniently performed on each sample by treatment of thiolesters (R_P,2*S*,3*S*)-**4g**and (S_P,2*S*,3*S*)-**4g**with an excess of $LiAlH_4$ (> 90% yield). The enantiomeric purity of the resulting thiols was then determined by HPLC analyses.[23]Thiol (R_P)-**2** generated from (R_P,2*S*,3*S*)-**4g** was enantiopure (ee = 100%), while its antipode (S_P)-**2**, arising from diastereoisomer (S_P,2*S*,3*S*)-**4g**, was isolated in 93% ee.[27] The absolute configurations were then unambiguously assigned by chemical correlation withknown rotation values.

In summary, we presentedin this account an *L*-isoleucine assisted resolution process, which provides operationally simple, convenient and cost-effective access to

[2.2]paracyclophane-4-thiol **2**as both(R_P) and (S_P) enantiomeric forms. Through thestraightforward formation of diastereoisomeric thiolesters **4g**, two fractional crystallizations furnished readily the less soluble compound of (R_P,2*S*,3*S*)configuration.[28] Isolation of the (S_P,2*S*,3*S*)-**4g** epimer was then achieved by a chromatographic separation(SiO_2).Removal of the chiral auxiliary by treatment with $LiAlH_4$ delivered the targetedmaterials (R_P)-**2** and (S_P)-**2**in good overall yield(~ 40% for each) and excellentenantiomeric purity (ee > 93%). Stereochemical assignments were supported by X-ray crystallography and polarimetry. The overall methodology constitutes a valuable addition to the few existing resolution protocols in this area. Our current investigations focus on the development of other planar chiral sulfur-based [2.2]paracyclophanes.

EXPERIMENTAL SECTION

General Experimental. Dry toluene, THF and CH_2Cl_2 were obtained by a passage down an activated alumina column. All other reagents and solvents were used as purchased from commercial sources. All reactions were performed in oven-dried glassware, under an atmosphere of dry nitrogen. Low reaction temperatures stated were those of the reaction mixtures. Reactions were purified by column chromatography with silica gel Si 60 (0.040–0.063 nm). Thin layer chromatography was carried out on silica gel 60 F_{254} (1.1 mm) with spot detection under UV light or by I_2 oxidation. Melting points were obtained on a capillary apparatus and are uncorrected. All chemical shifts (δ) and coupling constants (*J*) in the NMR spectra are quoted in parts per million (ppm) and Hertz (Hz) respectively. The following abbreviations are used to designate the multiplicity of the signals: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad and combinations thereof. The chemical shifts are calibrated to TMS (δ H 0.00) or residual proton and carbon resonances of the solvent $CDCl_3$ (δH 7.26 and δ C 77.16). IR spectra were recorded on an ATR-FT-IR instrumentequipped with a

diamond ATR probe. Mass spectra were obtained with a QTOF LC/MS instrument. Enantiomeric excesses were determined by chiral HPLC equipped with a photodiode array detector (200–400 nm) and an IA column (5 □m; size 250 × 4.6 mm). In all cases, the analysis was calibrated with a sample of the racemate. Optical rotations are reported in deg dm^{-1} cm^3 g^{-1} and were measured at room temperature (20 °C) on a polarimeter using a 1 mL cell with a 1 dm path length at 589 nm (sodium D light). (±)-[2.2]Paracyclophane-4-thiol (±)-**2** was prepared as previously reported by us.[17c]

Resolution Protocol with *L*-Leucine Derivative 3f.

(*2S*)-2-(1,3-Dioxoisoindolin-2-yl)-4-methylpentanoic Acid (5).[29] Phthalic anhydride (1.49 g, 8.00 mmol, 1 equiv), *L*-leucine (1.05 g, 8.00 mmol, 1 equiv) and triethylamine (0.11 mL, 0.8 mmol, 10 mol%) were dissolved in toluene (20 mL) and the resulting mixture was heated at reflux for 2 h. After cooling to room temperature, the volatiles were removed under vacuum. The resulting crude product was washed with an aqueous 1M HCl solution (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL) to give the desired carboxylic acid **5** as a white solid (1.79 g, 6.86 mmol, 86%). The material was pure enough to be used in the next step of the synthesis without further purification. mp: 120–122 °C. $[\alpha]_D^{20}$ –16.4 (*c* 0.1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.40–1.58 (m, 1H), 1.95 (ddd, *J* = 14.3, 10.1 and 4.4 Hz, 1H), 2.36 (ddd, *J* = 14.3, 11.5 and 4.1 Hz, 1H), 5.00 (dd, *J* = 11.5 and 4.4 Hz, 1H), 7.71–7.74 (m, 2H), 7.84–7.87 (m, 2H), 9.5–11 (very broad s, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 21.0, 23.1, 25.1, 37.0, 50.4, 123.6, 131.7, 134.2, 167.7, 175.7. IR (neat, ATR probe, cm^{-1}) ν: 2935, 1707 (C=O), 1465, 1384, 1288, 1276, 928, 717.

(*2S*)-2-(1,3-Dioxoisoindolin-2-yl)-4-methylpentanoyl Chloride (3f).[30] Carboxylic acid **5** (196 mg, 0.75 mmol, 1 equiv) and thionyl chloride (0.27 mL, 3.75 mmol, 5 equiv) were dissolved in toluene (10 mL). Three drops of DMF were added and the resulting mixture

was heated at reflux for 3 h. After cooling to room temperature, the volatiles were removed under vacuum to furnish the desired acid chloride **3f** as a dark yellow oil (209 mg, 0.75 mmol, quantitative). The product was used immediately in the next step without further purification. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.94 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 1.38–1.60 (m, 1H), 2.04 (ddd, J = 14.3, 10.0 and 4.3 Hz, 1H), 2.27–2.43 (m, 1H), 5.12 (dd, J = 11.1 and 4.3 Hz, 1H,), 7.72–7.74 (m, 2H), 7.84–7.87 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 21.0, 23.0, 25.1, 37.3, 59.1, 123.9, 131.5, 134.7, 167.0, 172.1.

Conversion into Thiolester 4f and Diastereoisomer Separation: Racemic [2.2]paracyclophane-4-thiol (±)-**2** (192 mg, 0.8 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (10 mL) at room temperature. A solution of freshly prepared acid chloride **3f** (1 mmol, 1.25 equiv) in CH_2Cl_2 (5 mL) and triethylamine (125µL, 0.88 mmol, 1.1 equiv) were successively added dropwise. The reaction mixture was stirred at room temperature for 20 h, washed successively with a saturated aqueous $NaHCO_3$ solution and water, dried over $MgSO_4$ and concentrated *in vacuo.* Purification of the resulting crude product by column chromatography (*n*-pentane/Et_2O, 80:20) allowed isolation of apure fraction of the less polar diastereoisomer (*R*$_P$,*S*)-**4f**(configuration assigned by an X-ray analysis). mp: 69–70 °C.**(*R*$_P$,*S*)-*S*-[2.2]Paracyclophan-4-yl 2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanethioate [(*R*$_P$,*S*)-4f].** TLC (*n*-pentane/Et_2O, 70:30) *Rf* = 0.48. $[\alpha]_D^{20}$–57.8 (*c* 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.95 (d, 6H, J = 6.5 Hz), 1.41–1.62 (m, 1H), 2.04 (ddd, J = 14.2, 10.0 and 4.3 Hz, 1H), 2.41 (ddd, J = 14.2, 11.3 and 4.1 Hz, 1H), 2.77–3.14 (m, 7H), 3.32 (ddd, J = 12.6, 9.7 and 2.8 Hz, 1H), 5.08 (dd, J = 11.3 and 4.3 Hz, 1H), 6.29–6.33 (m, 1H), 6.44–6.52 (m, 4H), 6.57–6.59 (m, 2H), 7.8–7.84 (m, 2H), 7.90–8.01 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 21.1, 23.2, 25.2, 34.2, 34.7, 34.9, 35.3, 37.0, 58.1, 123.8, 127.5, 130.1, 131.8, 132.2, 133.1, 133.3, 134.5, 134.7, 135.1, 138.9, 139.4, 139.5, 140.3, 143.9, 167.8, 194.6. MS (ESI) *m/z* (%)

989 [(2M + Na)$^+$, 15), 506 [(M + Na)$^+$, 53], 484 [(M + H)$^+$, 67], 216 (100) HRMS (ESI): calcd for $C_{30}H_{30}NO_3S$ $(MH)^+$ 484.1946, found 484.1952.

Removal of the Chiral Auxiliary to Furnish (R_P)-2: Thiolester(R_P,*S*)-**4f** (53 mg, 0.108 mmol) was dissolved in dry THF (1 mL). The resulting mixture was cooled to –78 °C and $LiAlH_4$ (49.6 mg, 1.34 mmol) was added portionwise. The solution was stirred for 15 min and the cold bath was removed. After stirring at room temperature for 24 h, the resulting mixture was poured into an aqueous 1M HCl (30 mL)/ice mixture. The precipitate was extracted with CH_2Cl_2 (3 × 40 mL) and the organic fractions were combined, dried over $MgSO_4$, filtered and evaporated to dryness. The resulting crude product was then purified by passing through a small plug of silica gel (*n*-pentane/CH_2Cl_2, 90:10) to afford thiol (R_P)-**2** as a colourless solid. Yield 96% (25.1 mg, 0.104 mmol, > 99% ee). mp: 139–141 °C (lit.[17c] mp 140 °C). $[\alpha]_D^{20}$–219.8 (*c* 0.01, $CHCl_3$). TLC (*n*-pentane/CH_2Cl_2, 90:10) *Rf* = 0.22. ^{1}H NMR ($CDCl_3$, 400 MHz) δ2.81 (ddd, *J*= 13.5, 10.6 and 6.0 Hz, 1H), 2.86–2.95 (m, 1H), 2.98–3.12 (m, 4H), 3.14 (s, 1H), 3.26 (ddd, *J*=13.0, 10.0 and 6.0 Hz, 1H), 3.37–3.47 (m, 1H), 6.21 (d, *J*=1.5 Hz, 1H), 6.37–6.49 (m, 3H), 6.50 and 6.60 (AB part of ABMX system, J_{AB} = 7.8, J_{AM} = 1.6 and J_{BX} =1.8 Hz, 2H), 7.21 (dd, *J*= 7.8 and 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 33.2, 34.8, 35.0, 35.5, 127.8, 130.6, 131.7, 132.1, 132.9, 133.5, 134.9, 135.7, 138.6, 139.3, 139.4, 140.5. IR (neat, ATR probe, cm^{-1}) ν: 713, 793, 804, 849, 897, 1059, 2925. MS (EI): *m/z*(%) 240 (M^+, 100), 207 (37), 136 (58), 121 (15), 104 (55), 91 (38), 78 (25). HPLC: t_R = 5.16 min; IA column (5 µm; size 250 × 4.6 mm); flow rate = 1.0 mL min^{-1}; *n*-heptane/EtOH/MeOH 95:2.5:2.5; 20 °C, 210 nm.

Resolution Protocol with*L*-Isoleucine Derivative 3g.

(2*S*,3*S*)-2-(1,3-Dioxoisoindolin-2-yl)-3-methylpentanoic Acid (6). [31] Phthalic anhydride (741 mg, 5 mmol, 1 equiv), *L*-isoleucine (659 mg, 5 mmol, 1 equiv) and

triethylamine (69 µl, 0.5 mmol) were dissolved in toluene (8 mL) and the resulting mixture was heated at reflux for 2 h. After cooling to room temperature, the volatiles were removed under vacuum. The resulting crude product was washed with an aqueous 1M HCl solution (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL) to give the desired carboxylic acid **6** as a white solid (1.28 g, 4.91 mmol, 98%): mp 107–109 °C (lit.[31] mp 123–125 °C). $[\alpha]_D^{20}$–28 (*c* 0.1, $CHCl_3$).^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (t, *J* = 7.4 Hz, 3H), 1.02–1.13 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.44–1.50 (m, 1H), 2.41–2.48 (m, 1H), 4.59 (d, *J* = 8.2 Hz, 1H), 7.70–7.77 (m, 2H), 7.84–7.89 (m, 2H), 8.80–10.15 (br s, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.9, 16.7, 25.8, 34.4, 57.1, 123.7, 131.6, 134.3, 167.8, 173.6. IR (neat, ATR probe, cm^{-1}) ν: 3223 (OH), 2966, 2930, 1770 (C=O), 1710 (C=O), 1610, 1466, 1385, 1190, 1082, 905, 719. HRMS (ESI, negative ionization mode) calcd for $C_{14}H_{14}NO_4$ $[M - H]^-$: 260.0923; found: 260.0919.

(2*S*,3*S*)-2-(1,3-Dioxoisoindolin-2-yl)-3-methylpentanoyl Chloride (3g).[30]In a round-bottomed flask, fitted with a condenser and a nitrogen inlet, carboxylic acid **3g** (199 mg, 0.76 mmol, 1 equiv) and thionyl chloride (0.28mL, 3.8 mmol, 5 equiv) were dissolved in dry toluene (10 mL). Three drops of DMF were added and the resulting mixture was heated at reflux for 3 h. After cooling to room temperature, the volatiles were removed under vacuum to furnish the desired acid chloride **3g** as a dark yellow oil (211 mg, 0.75 mmol, quantitative yield). The product was used directly in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, *J* = 7.4 Hz, 3H), 1.07–1.10 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.39–1.50 (m, 1H), 2.50–2.57 (m, 1H), 4.81 (d, *J* = 8.6 Hz, 1H), 7.79–7.93 (m, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.8, 16.5, 25.5, 35.1, 65.9, 124.0, 131.5, 134.7, 167.1, 169.9. IR (neat, ATR probe, cm^{-1}) ν: 2970, 1804 (C=O), 1716 (C=O), 1468, 1378, 1081, 873, 725.

Conversion into Thiolester 4g and Diastereoisomer Separation: Racemic [2.2]paracyclophane-4-thiol (±)-**2** (500 mg, 2.1 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (26 mL). A solution of freshly prepared acid chloride **3g** (733 mg, 2.6 mmol, 1.2 equiv) in dry

CH_2Cl_2 (13 mL) and triethylamine (320 µL, 2.3 mmol, 1.1 equiv) were added successively dropwise. The reaction mixture was stirred at room temperature for 48 h, washed successively with a saturated aqueous $NaHCO_3$ solution andwater, dried over $MgSO_4$and concentrated *in vacuo*. Fractional crystallization of the resulting crude product in a 4:1 *n*-heptane/$CHCl_3$ system (10 mL) led to the isolation of 295 mg of (*R*P,2*S*,3*S*)-**4g**. After concentration of the mother liquor, another crystallization was carried out with the same solvent combination (4 mL) to furnish 80 mg of (*R*P,2*S*,3*S*)-**4g**. A final purification of the residue by column chromatography on silica gel (*n*-pentane/Et_2O, 4:1) afforded successively 53 mg of (*R*P,2*S*,3*S*)-**4g** and 475 mg of(*S*P,2*S*,3*S*)-**4g**. All fractions of (*R*P,2*S*,3*S*)-**4g** were diastereopure. The sample of (*S*P,2*S*,3*S*)-**4g** issued from column chromatography was contaminated with 4% of epimer (*R*P,2*S*,3*S*)-**4g**. (*R*P,2*S*,3*S*)-**4g**(428 mg, 43% yield, dr of 100:0) and (*S*P,2*S*,3*S*)-**4g**(475 mg, 45% yield, dr of 96:4). Configurations of both diastereoisomers were deduced from those of the corresponding thiols **2** obtained after removal of the chiral auxiliary.

(*R*P,2*S*,3*S*)-*S*-[2.2]Paracyclophan-4-yl 2-(1,3-dioxoisoindolin-2-yl)-3-methylpentanethioate [(*R*P,2*S*,3*S*)-**4g].**Colourless solid. mp: 161–163 °C. $[\alpha]_D^{20}$–78.8 (*c* 0.1, $CHCl_3$).TLC (*n*-pentane/Et_2O, 80:20) *Rf* = 0.26. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 7.4 Hz, 3H), 0.99–1.08 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.37–1.51 (m, 1H), 2.64–2.75 (m, 1H), 2.78–3.13 (m, 7H), 3.24–3.37 (m, 1H), 4.77 (d, *J* = 9.2 Hz, 1H), 6.26–6.34 (m, 1H), 6.42 (s, 1H), 6.44–6.52 (m, 3H), 6.54–6.63 (m, 2H), 7.80–7.87 (m, 2H), 7.97–8.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.8, 17.0, 25.8, 33.9, 34.2, 34.8, 34.9, 35.4, 63.9, 123.9, 127.8, 130.0, 131.8, 132.2, 133.2, 133.3, 134.7, 134.7, 135.2, 138.6, 139.4, 139.6, 140.4, 144.1, 167.8, 193.2. IR (neat, ATR probe, cm^{-1}) ν: 2964, 2853, 1773 (C=O), 1719 (C=O), 1467, 1337, 1069, 908, 850, 747, 718. HRMS (ESI) calcd for $C_{30}H_{30}NO_3S[M + H]^+$: 484.1946; found: 484.1955.

(S_P,2*S*,3*S*)-*S*-[2.2]Paracyclophan-4-yl 2-(1,3-dioxoisoindolin-2-yl)-3-methylpentanethioate [(S_P,2*S*,3*S*)-**4g**]**.** Colourless solid. mp: 130–132 °C. $[\alpha]_D^{20}$–23.6 (*c* 0.1, $CHCl_3$).TLC (*n*-pentane/CH_2Cl_2, 80:20) *Rf* = 0.23. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.01–1.14 (m, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.41–1.53 (m, 1H), 2.68–2.79 (m, 1H), 2.81–2.91 (m, 1H), 2.91–3.12 (m, 6H), 3.24–3.34 (m, 1H), 4.81 (d, *J* = 9.3 Hz, 1H), 6.33 (dd, *J* = 7.7 and 0.9 Hz, 1H), 6.45 (s, 1H), 6.41–6.61 (m, 5H), 7.75–7.84 (m, 2H), 7.91–7.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.8, 16.9, 25.8, 33.8, 34.4, 34.8, 35.0, 35.4, 64.1, 123.9, 127.9, 130.4, 131.8, 132.4, 133.2, 133.3, 134.5, 134.7, 135.1, 139.1, 139.50, 139.55, 140.5, 143.5, 167.7, 192.9. IR (neat, ATR probe, cm^{-1}) ν: 3006, 2964, 2928, 2854, 1774 (C=O), 1716 (C=O), 1377, 1275, 1260, 906, 717. HRMS (ESI) calcd for $C_{30}H_{30}NO_3S$[M + H]$^+$: 484.1946; found: 484.1960.

Removal of the Chiral Auxiliary to Furnish (R_P)-2 and (S_P)-2: Thiolester (R_P,2*S*,3*S*)-**4g** or (S_P,2*S*,3*S*)-**4g** was dissolved in dry THF. The resulting mixture was cooled down to –78 °C and $LiAlH_4$ was added portionwise. The solution was stirred for 15 min and the cold bath was removed. After stirring at room temperature for 24 h, the resulting mixture was poured into an aqueous 1M HCl (30 mL)/ice mixture. The precipitate was extracted with CH_2Cl_2 (3 × 40 mL) and the organic fractions were combined, dried over $MgSO_4$, filtered and evaporated to dryness. The resulting crude product was then purified by column chromatography on silica gel (*n*-pentane/CH_2Cl_2, 90:10) to afford thiol (R_P)-**2** or (S_P)-**2** as a colourless solid.

(R_P)-**2:**Obtained according to the above procedure from (R_P,2*S*,3*S*)-**4g** (64.5 mg, 0.134 mmol) and $LiAlH_4$ (50.9 mg, 1.340 mmol) in THF (3 mL). Yield 95% (30.2 mg, 0.126 mmol, > 99% ee). The reaction was also conducted on a larger scale with (R_P,2*S*,3*S*)-**4g** (778 mg, 1.61 mmol) and $LiAlH_4$ (612 mg, 16.1 mmol) in THF (50 mL). Yield 82% (316 mg, 1.32 mmol, > 99% ee). Colourless solid. mp: 139–141 °C. $[\alpha]_D^{20}$–219.8 (*c* 0.01, $CHCl_3$). TLC (*n*-

pentane/CH_2Cl_2, 90:10) *Rf* = 0.22. Spectral data are similar to those already described for this enantiomer. HPLC: t_R = 5.16 min; IA column (5 µm; size 250 × 4.6 mm); flow rate = 1.0 mL min^{-1}; *n*-heptane/EtOH/MeOH 95:2.5:2.5; 20 °C, 210 nm.

(S_P)-**2:**Obtained from (S_P,2*S*,3*S*)-**4g** (64.5 mg, 0.134 mmol) and $LiAlH_4$ (50.9 mg, 1.340 mmol) in THF. Yield 90% (29 mg, 0.121 mmol, 93% ee). Colourless solid. mp: 139–141 °C. $[\alpha]_D^{20}$+198.4 (*c* 0.01, $CHCl_3$); [lit.[14b] $[\alpha]_D^{20}$+164 (*c* 1, $CHCl_3$) for a sample of 80% ee]. TLC (*n*-pentane/CH_2Cl_2, 90:10) *Rf* = 0.22. Spectral data are similar to those already described for enantiomer (R_P)-**2**. HPLC: t_R = 5.96 min; IA column (5 µm; size 250 × 4.6 mm); flow rate = 1.0 mL min^{-1}; *n*-heptane/EtOH/MeOH 95:2.5:2.5; 20 °C, 210 nm.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publication website at DOI:

Summary of resolution attempts of (±)-**2** with chiral auxiliaries **3**

Determination of the diastereoisomeric ratios of **4f**and **4g**by ^{1}H NMR

^{1}H and ^{13}C NMR spectra

HPLC chromatographs of (±)-**2**, (R_P)-**2** and (S_P)-**2**

CIF X-ray structure file for products (R_P,*S*)-**4f** and (R_P)-**2**

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We acknowledge financial support from ERDF funding (ISCE-Chem & INTERREG IVa program) and Synorg Labex. This work was also supported by the Crunch Network (interregional organic chemistry network Region Normandie),

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[15] The stereochemistry is maintained throughout the process and the enantiomeric excesses of (R_P)-**2 or** (S_P)-**2** reflect perfectly the enantiopurity of the precursors and of the intermediates.

[16] Deprotection was conveniently achieved in a single step through a fluoride-mediated desilylation in route a (quantitative yield), or a retro-Michael reaction initiated by a base in route c (yield > 95%). An unoptimized three-step sequence, including an initial and problematic reduction of the sulfinyl moiety into the corresponding sulfide, was described for route b, thus leading to a low 7% overall yield.

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[20] **3f** was efficiently prepared from *L*-leucine as described in the Experimental Section, *via* the corresponding *N*-phtalimido protected amino acid **5**.

[21] Rf values of 0.47 and 0.41 on an analytic TLC plate, development conditions: 70:30 *n*-pentane/diethyl ether mixture.

[22] (R_P,*S*)-**4f** is fully characterized in the Experimental Section.

[23] An amylose tris(3,5-dimethylphenylcarbamate) immobilized silica gel column (IA) was used.

[24] X-ray structure of (±)-**2** was previously reported in ref 12a.

[25] (S_P)-**2**was described previously as dextrorotatory by Rowlands ($[\alpha]_D^{20}$ +164.0for a sample of 80% ee). See Ref. 14b.

[26] Unfortunately, the reaction failed to proceed with kinetic resolution in $CH_2Cl_2$when using only 0.5 equiv of acyl chloride **3g**. A 1:1 ratio of the two possible diastereoisomers of **4g** was still observed.

[27] These values fitted with the purities of the individual precursors (R_P,2*S*,3*S*)-**4g** and (S_P,2*S*,3*S*)-**4g** previously determined by ^{1}H NMR spectroscopy.

[28] The resolution was also performed in a similar fashion, starting with a double amount of thiol (±)-**2** (1 g, 4.2 mmol). After a single crystallization of the crude product of **4g** (2.014 g, 4.2 mmol), a substantial amount of (R_P,2*S*,3*S*)-**4g** was already isolated (671 mg, 1.39 mmol, 33%, dr = 100:0).

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