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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S *Supporting Information*

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 the conversion into diastereoisomeric thiolesters and separation by two fractional crystallizations and column chromatography, was developed. Deprotection with LiAlH₄ 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 were confirmed by X-ray crystallography.
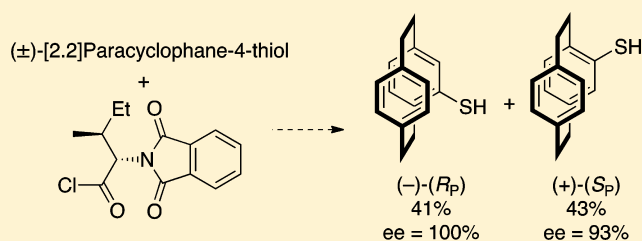
[2.2]Paracyclophane (PCP) **1** (R¹ = H) is the parent hydrocarbon for a fascinating family of organic compounds consisting of a rigid cofacial arrangement of two benzene units bridged at the *para* positions by CH₂CH₂ groups (Figure 1).[1]
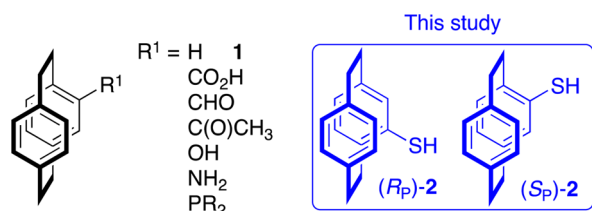

Figure 1. [2.2]Paracyclophane **1** and monosubstituted derivatives.

Following the pioneering reports by Brown, Farthing, and Cram more than 60 years ago,[2] the appealing structural, physical, and electronic properties of [2.2]PCP derivatives have resulted 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]

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 η⁶-arene transition-metal complexes, which require two substituents on an aromatic ring to become chiral, the presence of a single substituent on the [2.2]PCP skeleton is 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 nonracemic [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**, the derivatization of which inevitably furnishes a racemic mixture. Hence approaches to enantiopure [2.2]PCPs rely 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 conducted on the final target, or earlier on a precursor. As a consequence, further increases in the potential of planar chiral [2.2]PCPs is directly related to the availability by resolution of a pool of simple chiral [2.2]PCP-based building blocks. In this context, most privileged monosubstituted scaffolds possess a carbonyl[11a−c] [R¹ = CO₂H, CHO, C(O)CH₃] function, a hydroxyl[11d] (R¹ = OH), an amino[11e] (R¹ = NH₂), or a phosphino group[11f,g] (R¹ = PR₂) (Figure 1).

In retrospect, the case of a sulfur substituent has 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** (R¹ = SH) can rapidly be identified as a suitable chiral sulfur-based candidate (Figure 1). Access to a single enantiomer of (*R*ₚ)-**2** or (*S*ₚ)-**2** has been restricted to only three studies (Scheme

1).[14] Bräse used as starting material (R)-[2.2]paracyclophan-4-ol (ee >99%), previously obtained by enzymatic resolution of

Scheme 1. Previous Approaches to a Single Enantiomer of Thiol 2
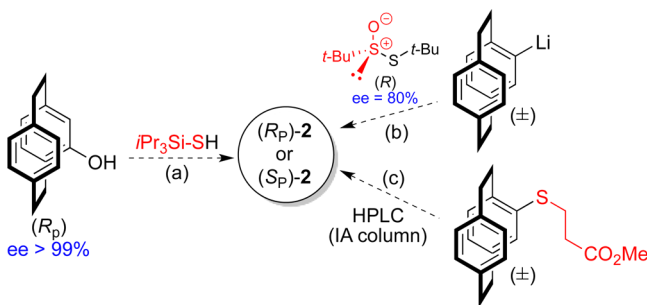
the racemic acetoxy analogue with *Candida cyclindracea* lipase.[14a] The sulfur atom was then introduced by a palladium cross-coupling reaction of the corresponding triflate with triisopropylsilanethiol (route a). Rowlands took profit from the Andersen approach and employed enantioenriched (R)-*tert*-butyl *tert*-butanethiosulfinate (ee = 80%, Ellman thiosulfinate) as both the sulfur source and chiral auxiliary.[14b] Reaction with (±)-4-lithio[2.2]paracyclophane furnished a 1:1 mixture of the two diastereoisomers of 4-*tert*-butylsulfinyl-[2.2]para-cyclophane, which were easily separated on a silica gel column (route b). More recently, our group described the separation of a racemic [2.2]PCP-based sulfanyl ester by semipreparative 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) or 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 acquire 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.

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 with 50 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%.

For chiral auxiliaries 3a−e, our efforts failed to find an eluent system, which would allow a practical level of separation of
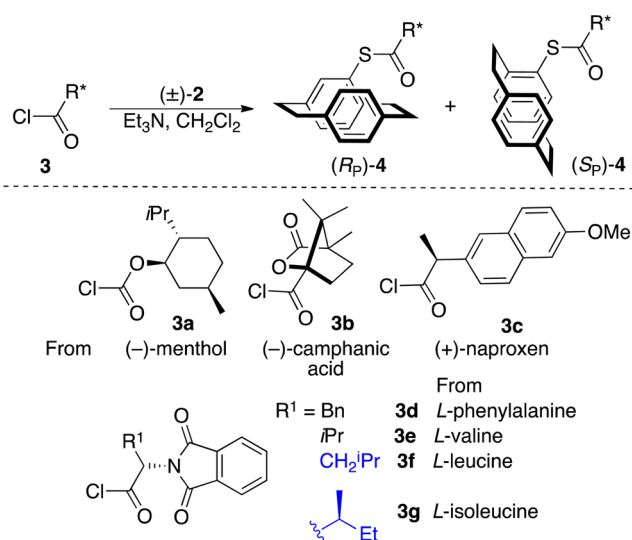

Figure 2. Chiral auxiliaries 3 tested for the resolution of (±)-2.

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 reduction with LiAlH$_4$ furnished thiol (−)-2 in 96% yield and with perfect enantiopurity, according to HPLC[23] chromatography. Much to our delight, single crystals of the diastereopure thiolester 4f, and also the corresponding enantiopure thiol (−)-2,[24] were suitable for X-ray analysis (Figure 3). They enabled a consistent assignment of configuration, with respectively a (R_P,S) stereochemistry for the isolated diastereoisomer of 4f and an (R_P) configuration for (−)-2 (Flack parameter = 0.03). This conclusion is also in perfect agreement with the specific rotation value of thiol (R_P)-2 determined as ([α]$_D^{20}$ −219.8).[25]

The resolution 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-isoleucine with phthalic anhydride, to furnish phthalimide derivative 6 in 98% yield. Subsequent reaction in the presence of SOCl$_2$ 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.

Racemic [2.2]paracyclophane-4-thiol (±)-2 and freshly prepared acid chloride 3g were then reacted at room temperature, in dichloromethane, in the presence of triethyl-amine. 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 α 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 later used 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
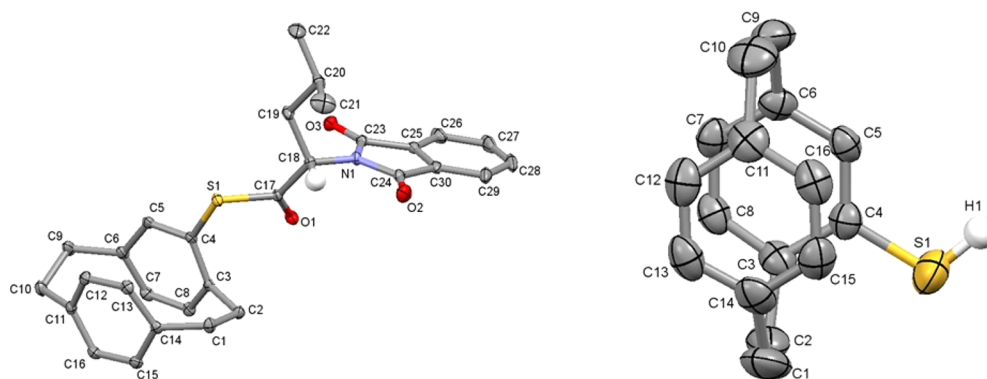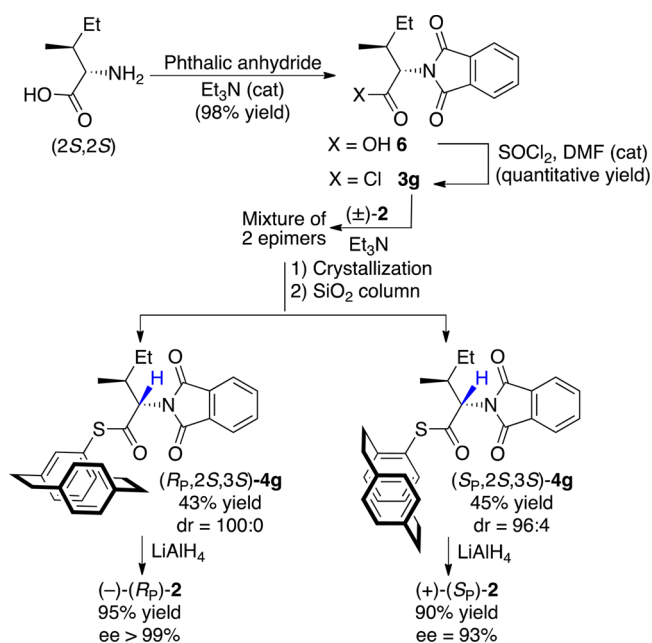
Figure 3. ORTEP diagrams of (R_P,S)-**4f** (left) and (R_P)-**2** (right) with ellipsoids shown at the 50% probability level. All hydrogen atoms have been omitted, except important ones.

Scheme 2. Resolution of (±)-2 with 3g Derived from L-Isoleucine

certain solvent ratios. This was exploited to develop an easy-to-use resolution process, in which a substantial amount of one diastereoisomer resulted from fractional crystallization. The simple protocol we have developed was optimized for 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 $(R_P,2S,3S)$-**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 $(R_P,2S,3S)$-**4g**. Finally, purification of the supernatant by column chromatography on silica gel with a 4:1 n-pentane/Et$_2$O mixture as eluent enabled the collection of an additional 53 mg of diastereoisomer $(R_P,2S,3S)$-**4g** (R_f of 0.26) in addition to 475 mg of diastereoisomer $(S_P,2S,3S)$-**4g** (R_f of 0.23). All fractions of $(R_P,2S,3S)$-**4g** were diastereopure. Diastereoisomer $(S_P,2S,3S)$-**4g** isolated after column chromatography was contaminated by only 4% of $(R_P,2S,3S)$-**4g**. In summary, this overall resolution protocol, combining two crystallizations and a chromatographic separation, led to the isolation of 428 mg of

$(R_P,2S,3S)$-**4g** (43% yield, dr = 100:0), while diastereoisomer $(S_P,2S,3S)$-**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 $(R_P,2S,3S)$-**4g** and $(S_P,2S,3S)$-**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 $(R_P,2S,3S)$-**4g** was enantiopure (ee = 100%), while its antipode (S_P)-**2**, arising from diastereoisomer $(S_P,2S,3S)$-**4g**, was isolated in 93% ee.[27] The absolute configurations were then unambiguously assigned by chemical correlation with known rotation values.

In summary, we presented in 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 the straightforward formation of diastereoisomeric thiolesters **4g**, two fractional crystallizations readily furnished the less soluble compound of $(R_P,2S,3S)$ configuration.[28] Isolation of the $(S_P,2S,3S)$-**4g** epimer was then achieved by a chromatographic separation (SiO$_2$). Removal of the chiral auxiliary by treatment with LiAlH$_4$ delivered the targeted materials (R_P)-**2** and (S_P)-**2** in good overall yield (~40% for each) and excellent enantiomeric 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$_2$Cl$_2$ were obtained by 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. The 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$_3$ (δ H 7.26 and δ C 77.16). IR spectra were recorded on an ATR-FT-IR instrument equipped 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 μm; size 250 mm × 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 1 M HCl solution (20 mL) and extracted with CH$_2$Cl$_2$ (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$_2$Cl$_2$ (10 mL) at room temperature. A solution of freshly prepared acid chloride **3f** (1 mmol, 1.25 equiv) in CH$_2$Cl$_2$ (5 mL) and triethylamine (125 μL, 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$_2$O, 80:20) allowed isolation of a pure 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$_2$O, 70:30) R_f = 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$_3$S (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 1 M HCl (30 mL)/ice mixture. The precipitate was extracted with CH$_2$Cl$_2$ (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$_2$Cl$_2$, 90:10) to afford thiol (R_P)-**2** as a colorless 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$_2$Cl$_2$, 90:10) R_f = 0.22. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.81 (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 mm × 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. *(2S,3S)-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 1 M HCl solution (20 mL) and extracted with CH$_2$Cl$_2$ (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.

(2S,3S)-2-(1,3-Dioxoisoindolin-2-yl)-3-methylpentanoyl Chloride (3g).[29] In a round-bottomed flask, fitted with a condenser and a nitrogen inlet, carboxylic acid **6** (199 mg, 0.76 mmol, 1 equiv) and thionyl chloride (0.28 mL, 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$_2$Cl$_2$ (26 mL). A solution of freshly prepared acid chloride **3g** (733 mg, 2.6 mmol, 1.2 equiv) in dry CH$_2$Cl$_2$ (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 and water, dried over MgSO$_4$, and concentrated *in vacuo*. Fractional crystallization of the resulting crude

product in a 4:1 *n*-heptane/CHCl₃ system (10 mL) led to the isolation of 295 mg of (R_P,2S,3S)-**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,2S,3S)-**4g**. A final purification of the residue by column chromatography on silica gel (*n*-pentane/Et₂O, 4:1) afforded successively 53 mg of (R_P,2S,3S)-**4g** and 475 mg of (S_P,2S,3S)-**4g**. All fractions of (R_P,2S,3S)-**4g** were diastereopure. The sample of (S_P,2S,3S)-**4g** issued from column chromatography was contaminated with 4% of epimer (R_P,2S,3S)-**4g**. (R_P,2S,3S)-**4g** (428 mg, 43% yield, dr of 100:0) and (S_P,2S,3S)-**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,2S,3S)-S-[2.2]Paracyclophan-4-yl 2-(1,3-dioxoisoindolin-2-yl)-3-methylpentanethioate [(R_P,2S,3S)-4g]. Colorless solid. Mp: 161–163 °C. $[\alpha]_D^{20}$ −78.8 (*c* 0.1, CHCl₃). TLC (*n*-pentane/Et₂O, 80:20) R_f = 0.26. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₃₀H₃₀NO₃S [M + H]⁺: 484.1946; found: 484.1955.

(S_P,2S,3S)-S-[2.2]Paracyclophan-4-yl 2-(1,3-dioxoisoindolin-2-yl)-3-methylpentanethioate [(S_P,2S,3S)-4g]. Colorless solid. Mp: 130–132 °C. $[\alpha]_D^{20}$ −23.6 (*c* 0.1, CHCl₃). TLC (*n*-pentane/CH₂Cl₂, 80:20) R_f = 0.23. ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (CDCl₃, 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 C₃₀H₃₀NO₃S [M + H]⁺: 484.1946; found: 484.1960.

Removal of the Chiral Auxiliary to Furnish (R_P)-2 and (S_P)-2. Thiolester (R_P,2S,3S)-**4g** or (S_P,2S,3S)-**4g** was dissolved in dry THF. The resulting mixture was cooled down to −78 °C, and LiAlH₄ 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 1 M HCl (30 mL)/ice mixture. The precipitate was extracted with CH₂Cl₂ (3 × 40 mL), and the organic fractions were combined, dried over MgSO₄, filtered, and evaporated to dryness. The resulting crude product was then purified by column chromatography on silica gel (*n*-pentane/CH₂Cl₂, 90:10) to afford thiol (R_P)-**2** or (S_P)-**2** as a colorless solid.

(R_P)-2: Obtained according to the above-mentioned procedure from (R_P,2S,3S)-**4g** (64.5 mg, 0.134 mmol) and LiAlH₄ (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,2S,3S)-**4g** (778 mg, 1.61 mmol) and LiAlH₄ (612 mg, 16.1 mmol) in THF (50 mL). Yield 82% (316 mg, 1.32 mmol, >99% ee). Colorless solid. Mp: 139–141 °C. $[\alpha]_D^{20}$ −219.8 (*c* 0.01, CHCl₃). TLC (*n*-pentane/CH₂Cl₂, 90:10) R_f = 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 mm × 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,2S,3S)-**4g** (64.5 mg, 0.134 mmol) and LiAlH₄ (50.9 mg, 1.340 mmol) in THF. Yield 90% (29 mg, 0.121 mmol, 93% ee). Colorless solid. Mp: 139–141 °C. $[\alpha]_D^{20}$ +198.4 (*c* 0.01, CHCl₃); [lit.[14b] $[\alpha]_D^{20}$ +164 (*c* 1, CHCl₃) for a sample of 80% ee]. TLC (*n*-pentane/CH₂Cl₂, 90:10) R_f = 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 mm × 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 Publications website at DOI: 10.1021/acs.joc.6b00560.

> Crystallographic data for (R_P)-**2**(CIF)
> Crystallographic data for (R_P,S)-**4f** (CIF)
> Summary of resolution attempts of (±)-**2** with chiral auxiliaries **3**; Determination of the diastereoisomeric ratios of **4f** and **4g** by ¹H NMR; ¹H and ¹³C NMR spectra; HPLC chromatographs of (±)-**2**, (R_P)-**2**, and (S_P)-**2** (PDF)

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Notes

The authors declare no competing financial interest.

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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) R_f 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 ($[\alpha]_D^{20}$ +164.0 for 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 ($R_P,2S,3S$)-**4g** and ($S_P,2S,3S$)-**4g** previously determined by ^1H 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 ($R_P,2S,3S$)-**4g** was already isolated (671 mg, 1.39 mmol, 33%, dr = 100:0).

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