

Functionalization of [2.2]Paracyclophanes via a Reductive Sulfanylation Reaction

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Cite This: <https://dx.doi.org/10.1021/acs.joc.0c02235>

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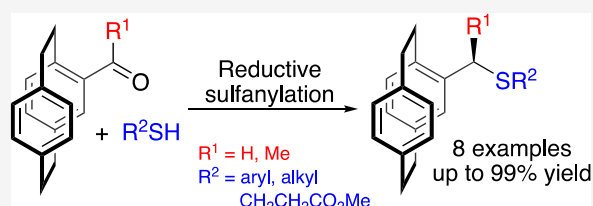
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ABSTRACT: An expeditious route to planar chiral sulfur-based scaffolds has been achieved in two operational steps from cheap and commercial [2.2]paracyclophane hydrocarbon. The sulfur atom was introduced in a specific benzylic position of the [2.2]paracyclophane according to a reductive sulfanylation reaction, which proceeds under two complementary reaction conditions with either the $\text{BF}_3 \cdot \text{OEt}_2 / \text{Et}_3\text{SiH}$ or $\text{TFA} / \text{BH}_3 \cdot \text{THF}$ combinations. The study was completed by the development of a highly efficient resolution approach by HPLC.



INTRODUCTION

Discovered by Brown and Farthing¹ 70 years ago, [2.2]-paracyclophane ([2.2]PCP) is the parent hydrocarbon of a fascinating family of organic scaffolds (Figure 1).² It involves a

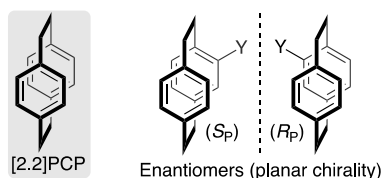


Figure 1. Parent [2.2]paracyclophane and planar chiral monosubstituted derivatives

compact arrangement of two cofacially stacked and strongly interacting benzene units, linked together at the *para* positions by ethylene groups. The unique structural, physical, and electronic properties of [2.2]PCP derivatives have resulted in significant attention.³ They have been successfully applied in numerous fields, such as energy materials, functional poly-*p*-xylylene (parylene) coatings, π -stacked polymers, and extensively used in asymmetric synthesis and catalysis.⁴ Indeed, an important facet of [2.2]PCP chemistry is related to the inherent planar chirality of these systems. The presence of a single substituent on the [2.2]PCP skeleton breaks the plane of symmetry of the molecule and generates enantiomers (Figure 1). As no asymmetric synthesis methods are available from the achiral [2.2]PCP hydrocarbon, approaches to enantiopure samples rely predominantly on the efficient resolution of racemates.⁵

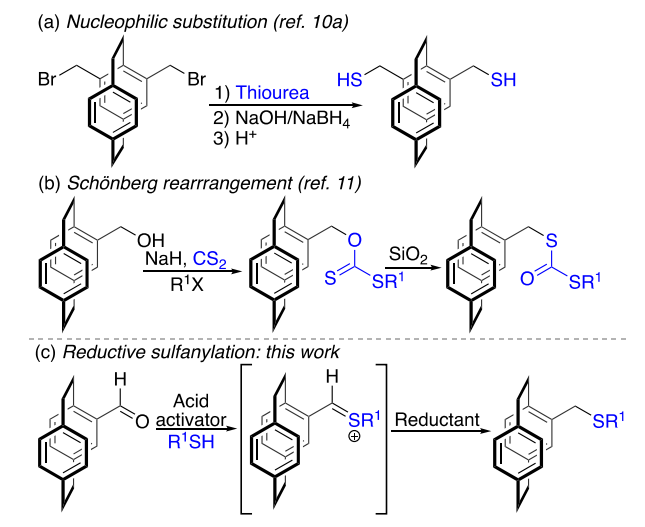
Despite the recent progress reported in selective functionalization of the [2.2]PCP core, unsolved synthetic challenges still remain, mainly due to the resistance they often exhibit for conventional chemical transformations.^{3a} Arguably, it is not

always possible to transfer well-established aromatic chemistry to the [2.2]PCP series, without being faced with low yields, uncontrolled regioselectivities, or unusual reactivities. As a consequence, special efforts are often required for optimization. Furthermore, [2.2]PCP derivatives exhibit a unique reactivity related to strong transannular interactions.

Inspired by our continuous interest in sulfur chemistry,⁶ we previously described the results of our investigations concerning the synthesis and the applications of monosubstituted sulfur-based [2.2]paracyclophanes.⁷ In the targeted structures, the heteroatom atom was directly attached to one aromatic deck of the [2.2]PCP ($Y = \text{SR}^1$, Figure 1). Considering the attractive reactivity of benzylic sulfur derivatives,⁸ we decided to turn our attention toward [2.2]PCP platforms, in which the sulfur center is located further from the ring, at a lateral benzylic position ($Y = \text{CH}_2\text{SR}^1$, Figure 1).⁹ However, to the best of our knowledge, literature precedents for this subclass of [2.2]PCP-based synthons remain surprisingly elusive. There are two common methodologies for the synthesis of such scaffolds, both of which provide racemic products. The most conventional one consists of a substitution reaction with the displacement of a benzylic halogen atom in the presence of a nucleophilic sulfur source¹⁰ (Scheme 1a), whereas the other takes profit of the specific reactivity of thiocarbonyl derivatives with the so-called benzylic Schönberg rearrangement¹¹ (thione-thiol transformation, Scheme 1b).

Received: September 16, 2020

Scheme 1. Literature Background and Strategy of this Work



Considering the versatile potential of these targets merging [2.2]PCP and benzylic heteroatom functionalities,¹² the development of a direct and practical strategy based on regioselective C–S bond formation on the [2.2]PCP platform is still warranted. An interesting feature would be to involve a readily available [2.2]PCP precursor, which could be prepared through a limited number of steps from the inexpensive and commercial [2.2]PCP hydrocarbon. As it is well established that the introduction of a carbonyl function to the [2.2]PCP core can be directly achieved through an electrophilic substitution, we postulated that a reductive reaction approach¹³ could then allow incorporation of the sulfur atom (Scheme 1c). Indeed, the reductive sulfenylation is an elegant but overlooked reaction, which involves the reduction of a thionium¹⁴ species, formed from an aldehyde or ketone in the presence of a thiol and an activator. A limited number of examples, employing a Lewis/Brønsted acid with either a hydrosilane or borane reductant, have been described.^{13,14} In light of this, we present the results of our investigations.

RESULTS AND DISCUSSION

The racemic [2.2]paracyclophane-4-carboxaldehyde **1** was prepared in a single operational step (Rieche formylation) from parent [2.2]PCP, as previously described by Bräse.¹⁵ The synthesis was easily scaled up and allowed the isolation of ~10 g of the substrate, from a single batch, in an excellent 85% yield.

In the initial study, thiophenol was chosen as the model sulfur reactant to optimize the reaction conditions (Table 1). In the first experiment (0.25 mmol scale), a stoichiometric amount of thiol and **1** was solubilized at 0 °C in CH₂Cl₂ (0.25 M). The reaction mixture was then reacted with commercial BF₃·2H₂O complex (2.1 equiv). After 5 min of reaction, triethylsilane (1.5 equiv) was added, and the reaction mixture was stirred at room temperature for 3 h. Analysis of the crude mixture by ¹H NMR clearly indicated the formation of the anticipated [2.2]PCP thioether **2a**, according to the presence of the diagnostic AX pattern of the diastereotopic protons of the CH₂S group (δ = 3.83 and 4.11 ppm, ²*J* = 12.4 Hz). Purification by chromatography on silica gel led to the isolation of **2a** in a satisfactory 75% yield (entry 1). The structure was then confirmed by X-ray crystal structure analysis. Switching to BF₃·OEt₂ as the Lewis acid furnished a

Table 1. Optimization of the Reaction Conditions for the Reductive Sulfenylation^a

entry	acid (equiv)	reductant (equiv)	solvent	yield (%)
1	BF ₃ ·2H ₂ O (2.1)	Et ₃ SiH (1.5)	CH ₂ Cl ₂	75
2	BF ₃ ·OEt ₂ (2.1)	Et ₃ SiH (1.5)	CH ₂ Cl ₂	83
3	BF ₃ ·OEt ₂ (1.1)	Et ₃ SiH (1.5)	CH ₂ Cl ₂	85 (83) ^b
4	BF ₃ ·OEt ₂ (1.1)	Et ₃ SiH (1.5)	DCE ^c	71
5	BF ₃ ·OEt ₂ (1.1)	Et ₃ SiH (1.5)	PhMe	75
6	BF ₃ ·OEt ₂ (1.1)	Et ₃ SiH (1.5)	THF	^d
7	CF ₃ CO ₂ H (15)	BH ₃ ·pyridine (1)	CH ₂ Cl ₂	80
8	CF ₃ CO ₂ H (15)	BH ₃ ·Me ₂ S (1)	CH ₂ Cl ₂	85
9	CF ₃ CO ₂ H (15)	BH ₃ ·THF (1)	CH ₂ Cl ₂	92 (88) ^b
10	CH ₃ CO ₂ H (15)	BH ₃ ·THF (1)	CH ₂ Cl ₂	^e
11	CF ₃ SO ₃ H (15)	BH ₃ ·THF (1)	CH ₂ Cl ₂	45
12	CF ₃ CO ₂ H (5)	BH ₃ ·THF (1)	CH ₂ Cl ₂	65 (80) ^f
13	CF ₃ CO ₂ H (1.1)	BH ₃ ·THF (1)	CH ₂ Cl ₂	^g

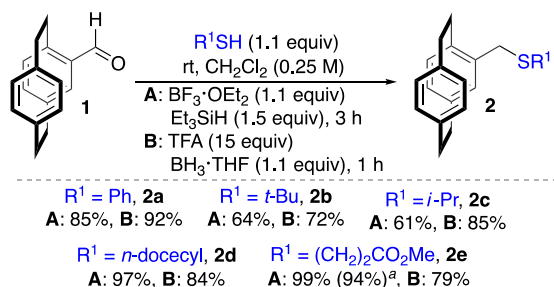
^aOptimization with 0.25 mmol of **1**. ^bIn brackets, reaction on a 1.2 mmol scale. ^cDCE = 1,2-dichloroethane. ^dComplex mixture. ^eNo reaction. ^fIn brackets, reaction with a concentration of 1 M. ^gReduction of **1** into the corresponding primary alcohol.

significant improvement to an 83% yield (entry 2). A similar reaction efficiency was observed employing a single equivalent of the BF₃·OEt₂ activator (entry 3). The effect of the solvent was then investigated. Whereas slightly lower yields (71 and 75%) were observed in 1,2-dichloroethane and toluene (entries 4 and 5), the reaction failed completely in a THF solution (entry 6).

We also explored activation by a Brønsted acid in the presence of a borane reductant. The use of a large excess of trifluoroacetic acid (TFA, 15 equiv) and BH₃·pyridine adduct (1 equiv) in CH₂Cl₂ furnished **2a** in a nice 80% yield (entry 7). A screening of other boron reagents and Brønsted acids was then investigated (entries 8–11). The best result was obtained in the presence of the TFA/BH₃·THF combination (92% yield, entry 9). Reducing the amount of TFA to 5 equiv had a detrimental effect on the reaction efficiency (65% yield, entry 12). However, increasing the concentration of aldehyde **1** from 0.25 to 1 M led to a much better 80% yield (entry 12). Finally, the use of a single equivalent resulted in no product **2a** formation (entry 13). To summarize, the conditions of entries 3 and 9 in Table 1 were determined to be optimal for the synthesis of **2a**. In both cases, no erosion of reaction efficiency was noticed when experiments were carried out on a larger 1.2 mmol scale (entries 3 and 9).

With optimal conditions in hand (conditions A with BF₃·OEt₂/Et₃SiH and B with TFA/BH₃·THF), the reaction scope with respect to the thiol was then investigated, as shown in Scheme 2. To our delight, the four aliphatic mercaptans tested reacted smoothly to afford the desired [2.2]PCP-based sulfides **2b–e** in good to excellent yields (64–99%). Worthy of note is the remarkable tolerance of the process to the ester function, with **2e** formed in a quantitative yield (conditions A). A comparison of the results obtained with both protocols shows the following trends. The use of conditions A is preferable with primary thiols (**2d** and **2e**), while conditions B brought about superior results with secondary, tertiary, and aromatic thiols

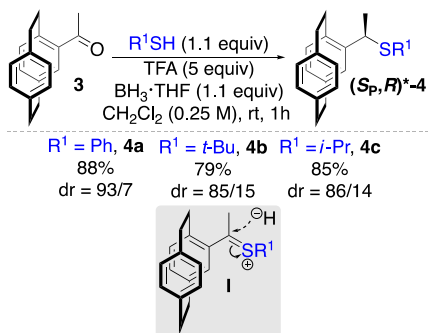
Scheme 2. Substrate Scope through Variation of the Thiol



^aIn brackets, yield at the 7.5 mmol scale.

(**2a–c**). To explore the synthetic utility of the method, a scale-up reaction (7.5 mmol) of the [2.2]PCP derivative **1a** with 3-sulfanylpropionic acid methyl ester ($\text{R}^1 = (\text{CH}_2)_2\text{CO}_2\text{Me}$) was then conducted under conditions A, delivering 2.4 g of thioether **2e** in an excellent 94% yield.

We turned our attention to extending the scope of this reductive sulfanylation reaction to the acetyl [2.2]PCP **3**, this offering a strategic entry to [2.2]PCP derivatives displaying both planar and central chirality (Scheme 3). This starting

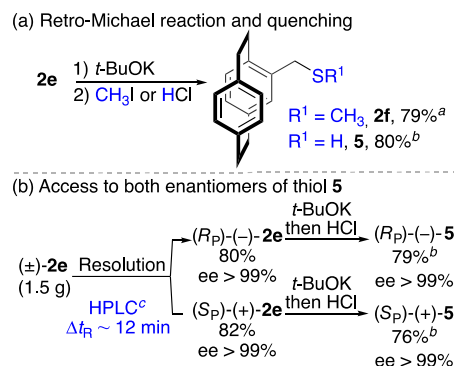
Scheme 3. Extension to 4-Acetyl[2.2]paracyclophane **3**

material was prepared in a 68% yield by Friedel–Crafts acylation of [2.2]PCP with acetyl chloride/ AlCl_3 in dry dichloromethane.¹⁶ A preliminary set of experiments employing thiophenol rapidly indicated that the TFA/ $\text{BH}_3 \cdot \text{THF}$ system was more appropriate in this series (see the Supporting Information). Furthermore, a decrease in the amount of TFA to 5 equiv markedly improved the reaction efficiency. The anticipated thioether **4a** was isolated in a pleasing 88% yield, as a mixture of two diastereoisomers in a 93/7 ratio. The products were readily separated by column chromatography on silica gel. Much to our delight, we succeeded in growing single crystals of the major diastereoisomer of **4a**, suitable for an X-ray diffraction analysis from which the relative (S_p, R)* stereochemistry was unambiguously assigned. *tert*-Butanethiol and isopropanethiol gave the desired products **4b** and **4c**, in 79% and 85% yields, respectively, along with a similar level of diastereoselectivity (ratios of ~85:15). Separation of the diastereoisomers was again efficient on silica gel, and the configurations were unambiguously assigned according to analytical similarities previously observed with **4a** (see the Supporting Information). To rationalize the preference for the (S_p, R)* configured products, we suggest that the reaction proceeds via thionium conformer **I**, with an attack of the reductant opposite to the CH_2CH_2 bridge (see the Supporting

Information for additional details of the transition state model).

Cross-experiments were then investigated with stoichiometric amounts of the [2.2]PCP-based aldehyde **1**, ketone **3**, and thiophenol (see the Supporting Information). Under the $\text{BF}_3 \cdot \text{OEt}_2/\text{Et}_3\text{SiH}$ conditions, the reductive sulfanylation is totally chemoselective for the aldehyde function (ratio **2a/4a** of 100:0). The reaction led essentially to the isolation of the phenylsulfanyl [2.2]PCP **2a**. With the TFA/ $\text{BH}_3 \cdot \text{THF}$ system, competing reactivity of the acetyl group was observed, but the process is still highly in favor of the formyl substituent (ratio **2a/4a** of 88:12).

The highly efficient formation of sulfanyl ester **2e** provided great opportunities to use this functionalized [2.2]PCP derivative as a generally usable sulfur building block, through a methodology productively used in our group before^{7a,b,17} and which consists of a retro-Michael reaction and further electrophilic trapping of the generated anion. Accordingly, the treatment of **2e** at low temperature (-78°C) with a 1 M solution of *t*-BuOK in THF (1.2 equiv) afforded the corresponding benzylic thiolate (Scheme 4a). *In situ* quench

Scheme 4. Useful Transformations of Sulfanyl Ester **2e**

^aWith 1.2 equiv of *t*-BuOK. ^bWith 2 equiv of *t*-BuOK. ^cDiacel Chiralpak IA column (id, 4.6 mm), *n*-heptane/EtOH (60:40 ratio), and a flow rate of 1.0 mL/min.

with iodomethane led to **2f** in a nice 79% yield. Notably, the synthesis of **2f** would have been problematic using the reductive sulfanylation reaction directly, as the use of gaseous methanethiol would have been required. Alternatively, quenching with an aqueous HCl solution afforded thiol **5** in an 80% yield. Thus, the precursor **2e** can be regarded as a valuable modular [2.2]PCP-based building block.

As already mentioned, approaches to enantiopure samples rely predominantly on the efficient resolution of racemates, which can be tedious, especially when larger quantities are needed. We attempted the resolution of our racemate (\pm)-**2e** on an analytical scale by chiral high-performance liquid chromatography (HPLC). Using a Diacel Chiralpak IA column (id, 4.6 mm), with a mixture of *n*-heptane and EtOH in a 60:40 ratio (v/v) and a flow rate of 1.0 mL/min, a tremendous difference in retention times of 12 min for enantiomer (R_p)-**2e** and (S_p)-**2e** was observed, resulting in a baseline separation of the two enantiomers (see the Supporting Information). These conditions were then successfully applied on a semipreparative-scale, from 1.5 g of starting material (Scheme 4b). This allowed the isolation of 596 mg of (R_p)-(-)-**2e** ($t_R = 5.96 \text{ min}$, 80%, ee > 99%) and 613 mg of (S_p)-(+)-**2e** ($t_R = 17.91 \text{ min}$, 82%, ee > 99%) (see the Supporting Information). Conversion

into the corresponding thiols, according to the aforementioned retro-Michael reaction, was then carried out with the individual enantiomers of **2e**. This allowed the isolation of each enantiomer of thiol **5** in good yields (79% and 76%), as enantiopure products (see the [Supporting Information](#)). A single crystal suitable for X-ray diffraction analysis was obtained on the enantiopure thiol, derived from the first-eluting enantiomer of sulfanyl ester **2e** obtained by chiral HPLC, and this established the configuration unambiguously as (*R_p*) (Flack parameter = −0.01). Given the wide reactivity of the sulfanyl group, this highly efficient resolution process provides a promising entry to a collection of sulfur-based [2.2]PCP derivatives in both enantiomeric forms.¹⁸

CONCLUSIONS

In conclusion, through combining a Friedel–Crafts reaction and a reductive sulfanylation, we have developed a reliable and high yielding method, which permits functionalization of the [2.2]PCP architecture at a specific benzylic position. Two complementary reaction conditions, promoted by either $\text{BF}_3 \cdot \text{OEt}_2/\text{Et}_3\text{SiH}$ or $\text{TFA}/\text{BH}_3 \cdot \text{THF}$ combinations, were developed. The methodology allowed efficient and straightforward access to a collection of relevant planar chiral sulfur-based [2.2]paracyclophanes. Furthermore, a highly efficient late-stage resolution of the planar chirality led to the isolation, in enantiopure forms, of both enantiomers of the related mercaptan, which can then serve as a versatile building block in the synthesis of more elaborated [2.2]PCP derivatives. These original scaffolds with the key features they display possess many application options that are to be explored.

EXPERIMENTAL SECTION

General Experimental. Dry 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. Due to the stench of thiols, all glassware and syringes were washed with bleach after use. 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 mm). 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; 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. Semipreparative separations of enantiomers were carried out on a chromatographic system with a 5 mL sample loop, equipped with a photodiode array detector (200–400 nm), and an IA column (5 mm; size 250 mm \times 20 mm). Enantiomeric excesses were determined by chiral HPLC equipped with a photodiode array detector (200–400 nm) and an IA column (5 mm; size 250 mm \times 4.6 mm). In all cases, the analysis was calibrated with a sample of the racemate. Optical rotations are reported in $\text{deg dm}^{-1} \text{cm}^3 \text{g}^{-1}$ 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).

Synthesis of the [2.2]PCP-Based Precursors. [2.2]-Paracyclophane-4-carboxaldehyde (**1**).¹⁵ The synthesis was carried out as reported in the literature. To a solution of [2.2]paracyclophane (10 g, 48 mmol, 1 equiv) in CH_2Cl_2 (450 mL) cooled to 0 °C, were

successively added TiCl_4 (17.6 g, 92.8 mmol, 2 equiv, 10.2 mL) and $\text{Cl}_2\text{CHOCH}_3$ (4.5 mL, 50.8 mmol, 1 equiv). The resulting mixture was allowed to warm up slowly to room temperature and then stirred at this temperature for 6 h. Water (450 mL) was then added and stirring was maintained for 2 h. The reaction mixture was extracted with CH_2Cl_2 , and the combined organic phases were dried over MgSO_4 , filtered, and evaporated. The resulting solid was purified by column chromatography on silica gel with dichloromethane as an eluent to obtain the desired aldehyde **1**. Yield: 85% (9.61 g, 0.04 mol). White solid. Mp: 148–149 °C (lit.¹⁵ mp: 159 °C). TLC ($\text{CH}_2\text{Cl}_2/\text{pentane}$, 80:20) R_f = 0.59. ^1H NMR (400 MHz, CDCl_3): δ 9.96 (s, 1H), 7.01 (d, *J* = 1.8 Hz, 1H), 6.73 (dd, *J* = 7.8 and 1.8, 1H), 6.61–6.54 (m, 2H), 6.49 (dd, *J* = 7.8 and 1.6, 1H), 6.44 and 6.39 (AB part of ABXY pattern, *J* = 7.8 and 1.6, 1H each), 4.10 (ddd, *J* = 12.2, 10.3 and 1.8, 1H), 2.91–3.31 (m, 7H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 192.1, 143.4, 140.8, 139.5, 139.6, 138.2, 136.7, 136.5, 136.3, 133.4, 133.1, 132.5, 132.3, 35.4, 35.3, 35.1, 33.8. IR (cm^{-1}): 1719, 795, 875, 906, 1227, 1410, 1590, 1677 (C=O), 2751, 2850, 2925. MS (EI): *m/z* (%) 236 (84), 144 (21), 132 (21), 104 (100), 78 (38). HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{17}\text{O}$ [*M* + *H*]⁺, 237.1279; found, 237.1268.

4-Acetyl[2.2]paracyclophane (3).¹⁶ In two-necked round-bottomed flask, equipped with a nitrogen inlet, a solution of [2.2]paracyclophane (4.16 g, 20 mmol, 1 equiv) in dry CH_2Cl_2 (22 mL) was cooled to −50 °C. A solution of acetyl chloride (3 mL, 42 mmol, 2.1 equiv) and AlCl_3 (4.67 g, 35 mmol, 1.75 equiv) was added dropwise. After stirring at −50 °C for 15 min, the reaction mixture was allowed to warm to −20 °C and stirred at this temperature for an additional 15 min. The resulting mixture was poured into an aqueous 6 N HCl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 \times 30 mL). 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 ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 99:1) to afford the expected ketone **3**. Yield: 68% (3.40 g, 13.6 mmol). White solid. Mp: 100–101 °C (lit.¹⁶ mp: 107–109 °C). TLC ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 99:1) R_f = 0.7. ^1H NMR (400 MHz, CDCl_3): δ 6.93 (d, *J* = 1.8, 1H), 6.66 (dd, *J* = 7.9 and 1.8, 1H), 6.58–6.49 (m, 4H), 6.39 (dd, *J* = 7.9 and 1.9), 3.98 (ddd, *J* = 12.6, 7.0 and 4.6, 1H), 3.25–3.11 (m, 4H), 3.10–2.97 (m, 2H), 2.90–2.79 (m, 1H), 2.47 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 200.5, 141.8, 140.5, 140.0, 139.4, 138.1, 136.65, 136.60, 134.4, 133.3, 133.1, 132.3, 131.4, 36.3, 35.4, 35.3, 35.1, 29.0. IR (cm^{-1}): 731, 793, 854, 902, 1185, 1266, 1349, 1552, 1679 (C=O), 2888, 2850, 2922, 2951. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{19}\text{O}$ [*M* + *H*]⁺: 251.1436; found, 251.1441.

Synthesis of the [2.2]PCP-Based Sulfides 2. General Procedure A: $\text{BF}_3 \cdot \text{OEt}_2/\text{Et}_3\text{SiH}$ -Mediated Reductive Sulfanylation. In a two-necked round-bottomed flask, equipped with a nitrogen inlet, a 0.25 M solution of [2.2]paracyclophane-4-carboxaldehyde **1** (1 equiv) in CH_2Cl_2 and the appropriate thiol (1.1 equiv) were successively introduced. The stirred mixture was then charged successively dropwise with $\text{BF}_3 \cdot \text{OEt}_2$ (1.1 equiv) and triethylsilane (1.5 equiv). The reaction was then stirred at room temperature for an additional 3 h. After the addition of a saturated NaHCO_3 aqueous solution, extraction with CH_2Cl_2 (20 mL), the organic layer was washed with H_2O (20 mL). The collected aqueous layers were extracted with CH_2Cl_2 (2 \times 20 mL). 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 to afford the anticipated sulfide **2**.

General Procedure B: $\text{CF}_3\text{CO}_2\text{H}/\text{BH}_3 \cdot \text{THF}$ -Mediated Reductive Sulfanylation. In a two-necked round-bottomed flask, equipped with a nitrogen inlet, a 0.25 M solution of [2.2]paracyclophane-4-carboxaldehyde **1** (1 equiv) in CH_2Cl_2 and the appropriate thiol (1.1 equiv) were introduced. The stirred mixture was then charged dropwise successively with trifluoroacetic acid (15.6 equiv) and $\text{BH}_3 \cdot \text{THF}$ (1.1 equiv). The reaction was then stirred at room temperature for an additional hour. After the addition of an aqueous saturated NaHCO_3 solution, extraction with CH_2Cl_2 (20 mL), the organic layer was washed with H_2O (20 mL). The collected aqueous layers were

extracted with CH_2Cl_2 (2×20 mL). 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 to afford the anticipated sulfide 2.

4-(Phenylsulfanyl)methyl[2.2]paracyclophane (2a). The compound was obtained following general procedure A from aldehyde 1 (150 mg, 0.63 mmol), thiophenol ($\text{R}^1 = \text{Ph}$, 71 μL , 0.70 mmol), $\text{BF}_3 \cdot \text{OEt}_2$ (86 μL , 0.70 mmol), and triethylsilane (152 μL , 0.94 mmol) in CH_2Cl_2 (2.5 mL). Yield: 85% (177.9 mg, 0.54 mmol). The compound obtained following general procedure B from aldehyde 1 (59 mg, 0.25 mmol), thiophenol ($\text{R}^1 = \text{Ph}$, 28 μL , 0.275 mmol), trifluoroacetic acid (300 μL , 3.9 mmol), and $\text{BH}_3 \cdot \text{THF}$ (1 M solution, 275 μL , 0.275 mmol) in CH_2Cl_2 (1 mL). Yield: 92% (76 mg, 0.54 mmol). White solid. Mp: 88–89 °C. TLC (pentane/ CH_2Cl_2 , 70:30) $R_f = 0.56$. ^1H NMR (500 MHz, CDCl_3): δ 7.34–7.23 (m, 4H), 7.22–7.15 (m, 1H), 6.72 (dd, $J = 7.8$ and 1.8, 1H), 6.58 (dd, $J = 7.8$ and 1.8, 1H), 6.55–6.48 (m, 3H), 6.45 (dd, $J = 7.8$ and 1.8, 1H), 6.37 (s, 1H), 4.11 (d, $J = 12.4$, 1H), 3.83 (d, $J = 12.4$, 1H), 3.43 (ddd, $J = 13.7$, 10.8 and 6.0, 1H), 3.22–3.12 (m, 1H), 3.12–2.93 (m, 5H), 2.86 (ddd, $J = 13.7$, 10.8 and 6.0, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 140.2, 139.7, 139.4, 138.1, 137.1, 136.2, 135.3, 135.0, 133.5, 133.4, 132.3, 132.0, 129.6, 129.0, 128.9, 126.2, 38.1, 35.4, 35.1, 34.5, 33.4. IR (cm^{-1}): 714, 796, 897, 1412, 1485, 1592, 2849, 2922, 3006. HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{22}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 353.1340; found, 353.1338.

4-(tert-Butylsulfanyl)methyl[2.2]paracyclophane (2b). Obtained following the general procedure A from aldehyde 1 (150 mg, 0.63 mmol), *tert*-butanethiol ($\text{R}^1 = t\text{-Bu}$, 78 μL , 0.70 mmol), $\text{BF}_3 \cdot \text{OEt}_2$ (86 μL , 0.70 mmol) and triethylsilane (152 μL , 0.94 mmol) in CH_2Cl_2 (2.5 mL). Yield: 64% (125.62 mg, 0.40 mmol). Obtained following general procedure B from aldehyde 1 (118 mg, 0.5 mmol), *t*-butanethiol ($\text{R}^1 = t\text{-Bu}$, 62 μL , 0.55 mmol), trifluoroacetic acid (580 μL , 7.5 mmol), and $\text{BH}_3 \cdot \text{THF}$ (1 M solution, 550 μL , 0.55 mmol) in CH_2Cl_2 (2 mL). Yield: 72% (112 mg, 0.36 mmol). White solid. Mp: 81–82 °C. TLC (pentane/ CH_2Cl_2 , 80:20) $R_f = 0.34$. ^1H NMR (400 MHz, CDCl_3): δ 6.70 (dd, $J = 7.8$ and 1.6, 1H), 6.54 and 6.50 (AB part of ABMX pattern, $J_{\text{AB}} = 7.9$, $J_{\text{AM}} = 1.6$ and $J_{\text{BX}} = 1.7$, 2H), 6.48–6.41 (m, 3H), 6.31 (s, 1H), 3.71 (d, $J = 12.0$, 1H), 3.47* (d, $J = 12.0$, 1H), 3.53–3.42* (m, 1H) (* signals overlapping), 3.23–3.13 (m, 1H), 3.13–2.93 (m, 5H), 2.88 (ddd, $J = 13.5$, 10.8 and 6.3, 1H), 1.35 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 140.0, 139.7, 139.4, 137.9, 137.5, 135.3, 135.1, 133.5, 133.4, 132.3, 131.6, 128.9, 42.6, 35.4, 35.1, 34.6, 33.5, 32.4, 31.0. IR (cm^{-1}): 715, 796, 870, 903, 1159, 1363, 1411, 1434, 1458, 1593, 2853, 2923, 3007. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{26}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 333.1653; found 333.1663. Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{S}$: C, 81.23; H, 8.44; S, 10.33. Found: C, 81.42; H, 8.31; S, 10.30.

4-(Isopropylsulfanyl)methyl[2.2]paracyclophane (2c). The compound was obtained following general procedure A from aldehyde 1 (59 mg, 0.25 mmol), isopropanethiol ($\text{R}^1 = i\text{-Pr}$, 26 μL , 0.275 mmol), $\text{BF}_3 \cdot \text{OEt}_2$ (33 μL , 0.275 mmol), and triethylsilane (60 μL , 0.375 mmol) in CH_2Cl_2 (1 mL). Yield: 61% (45 mg, 0.15 mmol). The compound was obtained following general procedure B from aldehyde 1 (118 mg, 0.5 mmol), isopropanethiol ($\text{R}^1 = i\text{-Pr}$, 52 μL , 0.55 mmol), trifluoroacetic acid (580 μL , 7.5 mmol), and $\text{BH}_3 \cdot \text{THF}$ (1 M solution, 550 μL , 0.55 mmol) in CH_2Cl_2 (2.2 mL). Yield: 85% (126 mg, 0.425 mmol). White solid. Mp: 49–51 °C. TLC (pentane/ CH_2Cl_2 , 4:1) $R_f = 0.30$. ^1H NMR (400 MHz, CDCl_3): δ 6.69 (dd, $J = 7.9$ and 1.7, 1H), 6.55 and 6.50 (AB part of ABMX pattern, $J_{\text{AB}} = 7.8$, $J_{\text{AM}} = 1.7$ and $J_{\text{BX}} = 1.8$, 2H), 6.48–6.45 (m, 2H), 6.43 (dd, $J = 7.9$ and 1.8, 1H), 6.30 (s, 1H), 3.72 (d, $J = 13.2$, 1H), 3.45* (d, $J = 13.2$, 1H), 3.53–3.44* (m, 1H) (* signals overlapping), 3.24–3.13 (m, 1H), 3.13–2.94 (m, 5H), 2.87 (ddd, $J = 13.5$, 10.7 and 6.1, 1H), 2.69 (sept, $J = 6.8$, 1H), 1.24 (d, $J = 6.8$, 3H), 1.21 (d, $J = 6.8$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 139.9, 139.6, 139.4, 137.95, 137.90, 135.3, 135.0, 133.5, 133.3, 132.2, 131.5, 128.9, 35.4, 35.1, 34.6, 34.5, 34.1, 33.5, 23.4 (a single signal for the two CH_3 of the *i*-Pr group). IR (cm^{-1}): 715, 795, 870, 900, 1051, 1154, 1241, 1411, 1451, 1593, 2853, 2924, 2951. HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{24}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 319.1496; found, 319.1504.

4-(Dodecylsulfanyl)methyl[2.2]paracyclophane (2d). The compound was obtained following general procedure A from aldehyde 1 (150 mg, 0.63 mmol), dodecane-1-thiol ($\text{R}^1 = \text{CH}_3(\text{CH}_2)_{11}$, 166 μL , 0.70 mmol), $\text{BF}_3 \cdot \text{OEt}_2$ (86 μL , 0.70 mmol), and triethylsilane (152 μL , 0.94 mmol) in CH_2Cl_2 (2.5 mL). Yield: 97% (259.4 mg, 0.61 mmol). The compound was obtained following general procedure B from aldehyde 1 (118 mg, 0.5 mmol), dodecane-1-thiol ($\text{R}^1 = \text{CH}_3(\text{CH}_2)_{11}$, 132 μL , 0.55 mmol), trifluoroacetic acid (580 μL , 7.5 mmol), and $\text{BH}_3 \cdot \text{THF}$ (1 M solution, 550 μL , 0.5 mmol) in CH_2Cl_2 (2.2 mL). Yield: 84% (177 mg, 0.42 mmol). White solid. Mp: 54–55 °C. TLC (pentane/ CH_2Cl_2 , 80:20) $R_f = 0.45$. ^1H NMR (400 MHz, CDCl_3): δ 6.68 (dd, $J = 7.9$ and 1.6, 1H), 6.56–6.41 (m, 5H), 6.28 (s, 1H), 3.71 (d, $J = 13.2$, 1H), 3.52–3.43 (m, 1H), 3.40 (d, $J = 13.2$, 1H), 3.24–3.13 (m, 1H), 3.12–2.94 (m, 5H), 2.93–2.81 (m, 1H), 2.32 (t, $J = 7.4$, 2H), 1.58–1.44 (m, 2H), 1.39–1.19 (m, 18H), 0.92 (t, $J = 6.9$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 139.9, 139.6, 139.4, 137.95, 137.90, 135.25, 135.20, 133.5, 133.3, 132.2, 131.5, 129.0, 35.4, 35.2, 35.1, 34.5, 33.5, 32.0, 31.7, 29.85, 29.80, 29.7, 29.6, 29.55, 29.50, 29.3, 29.0, 22.8, 14.3. IR (cm^{-1}): 717, 798, 872, 903, 945, 1412, 1432, 1464, 1593, 2850, 2919, 2949, 3007. HRMS (ESI): calcd for $\text{C}_{29}\text{H}_{42}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 445.2905; found, 445.2925.

3-([2.2]Paracyclophan-4-yl)methylsulfanylpropionic Acid Methyl Ester (2e). The compound was obtained following general procedure A from aldehyde 1 (150 mg, 0.63 mmol), 3-sulfanylpropionic acid methyl ester ($\text{R}^1 = (\text{CH}_2)_2\text{CO}_2\text{Me}$, 77 μL , 0.70 mmol), $\text{BF}_3 \cdot \text{OEt}_2$ (86 μL , 0.70 mmol), and triethylsilane (152 μL , 0.94 mmol) in CH_2Cl_2 (2.5 mL). Yield: 99% (213.5 mg, 0.63 mmol). The compound was obtained following general procedure B from aldehyde 1 (118 mg, 0.5 mmol), 3-sulfanylpropionic acid methyl ester ($\text{R}^1 = (\text{CH}_2)_2\text{CO}_2\text{Me}$, 61 μL , 0.55 mmol), trifluoroacetic acid (580 μL , 7.5 mmol), and $\text{BH}_3 \cdot \text{THF}$ (1 M solution, 550 μL , 0.55 mmol) in CH_2Cl_2 (2 mL). Yield: 79% (135 mg, 0.4 mmol). White solid. Mp: 58–59 °C. TLC (pentane/ EtOAc , 80:20) $R_f = 0.45$. ^1H NMR (400 MHz, CDCl_3): δ 6.65 (dd, $J = 7.8$ and 1.8, 1H), 6.55–6.43 (m, 4H), 6.41 (dd, $J = 7.8$ and 1.8, 1H), 6.26 (s, 1H), 3.72 (d, $J = 13.3$, 1H), 3.67 (s, 3H), 3.42* (d, $J = 13.3$, 1H), 3.48–3.39* (m, 1H) (* signals overlapping), 3.22–3.12 (m, 1H), 3.12–2.94 (m, 5H), 2.86 (ddd, $J = 13.6$, 10.2 and 6.2, 1H), 2.61–2.57 (m, 2H), 2.51–2.46 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 172.4, 140.0, 139.5, 139.3, 137.9, 137.2, 135.3, 135.1, 133.5, 133.3, 132.2, 131.7, 128.9, 51.8, 35.3, 35.2, 35.0, 34.5, 34.4, 33.4, 26.4. IR (cm^{-1}): 715, 794, 1238, 1344, 1434, 1592, 1724 ($\text{C}=\text{O}$), 2851, 2924, 3005. MS (ESI): m/z (%) 703 [(2M + Na) $^+$, 31], 363 [(M + Na) $^+$, 100], 341 [(MH) $^+$, 38], 231 (29), 221 (79). HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{25}\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$, 341.1575; found, 341.1576. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{O}_2\text{S}$: C, 74.08; H, 7.11; S, 9.42. Found: C, 74.00; H, 7.17; S, 9.83.

Gram-Scale Synthesis of 2e. A two-necked round-bottomed flask, equipped with a nitrogen inlet, was charged successively with [2.2]paracyclophane-4-carboxaldehyde 1 (1.77 g, 7.5 mmol, 1 equiv), 3-sulfanylpropionic acid methyl ester (918 μL , 8.25 mmol 1.1 equiv), and CH_2Cl_2 (30 mL). The resulting mixture cooled in an ice bath, and $\text{BF}_3 \cdot \text{OEt}_2$ (1.02 mL, 8.25 mmol, 1.1 equiv) was added. After 5 min, triethylsilane (1,815 mL, 11,25 mmol, 1.5 equiv) was added. After removal of the cold bath, the reaction mixture was allowed to stir at room temperature for 3 h. After the addition of a saturated NaHCO_3 aqueous solution, extraction with CH_2Cl_2 (20 mL), the organic layer was washed with H_2O (2×20 mL). The collected aqueous layers were extracted with CH_2Cl_2 (3×20 mL). 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 with pentane/ethyl acetate (9:1) to give sulfide 2e (2.4 g, 94%).

Synthesis of the [2.2]PCP-Based Sulfides 4. General Procedure. In a two-necked round-bottomed flask, equipped with a nitrogen inlet, a 0.25 M solution of 4-acetyl[2.2]paracyclophane 3 (1 equiv) in CH_2Cl_2 and the appropriate thiol (1.1 equiv) were introduced. The stirred mixture was successively charged dropwise with trifluoroacetic acid (5 equiv) and $\text{BH}_3 \cdot \text{THF}$ (1.1 equiv). The reaction was then stirred at room temperature for an additional hour. After the addition of a saturated NaHCO_3 aqueous solution,

extraction with CH_2Cl_2 (20 mL), the organic layer was washed with H_2O (20 mL). The collected aqueous layers were extracted with CH_2Cl_2 (2 \times 20 mL). 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 to afford the anticipated sulfide **4**.

4-[1'-(Phenylsulfanyl)ethyl][2.2]paracyclophane (4a). The compound was obtained following the general procedure from ketone **3** (500 mg, 2 mmol), thiophenol ($\text{R}^1 = \text{Ph}$, 215 μL , 2.1 mmol), trifluoroacetic acid (750 μL , 10 mmol), and $\text{BH}_3\cdot\text{THF}$ (1 M solution, 2.1 mL, 2.1 mmol) in CH_2Cl_2 (10 mL) as a mixture (93:7 ratio) of diastereoisomers. Yield: 88% (604 mg, 1.76 mmol). Separation was achieved by column chromatography on silica gel (pentane/ CH_2Cl_2 , 90:10). (S_p,R)*-**4a** (major diastereoisomer). White solid. Mp: 111–112 °C. TLC (pentane/ CH_2Cl_2 , 90:10) $R_f = 0.08$. ^1H NMR (400 MHz, CDCl_3): δ 7.36–7.30 (m, 2H), 7.29–7.24 (m, 3H), 6.55–6.46 (m, 5H), 6.40–6.35 (m, 1H), 6.29 (s, 1H), 4.33 (q, $J = 6.8$, 1H), 3.66 (ddd, $J = 13.6$, 10.1 and 1.9, 1H), 3.27–3.17 (m, 1H), 3.15–2.88 (m, 6H), 1.67 (d, $J = 6.8$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 140.0, 139.75, 139.70, 139.5, 138.3, 135.6, 134.8, 133.7, 133.5, 133.1, 132.15, 132.10, 130.4, 129.6, 128.8, 127.6, 44.5, 35.4, 35.3, 34.7, 33.9, 19.1. IR (cm^{-1}): ν : 738, 861, 1180, 1372, 1412, 1437, 1477, 1583, 1592, 2852, 2926, 3008. HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{24}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 367.1496; found, 367.1499. (S_p,S)*-**4a** (minor diastereoisomer). Colorless oil. TLC (pentane/ CH_2Cl_2 , 90:10) $R_f = 0.16$. ^1H NMR (400 MHz, CDCl_3): δ 7.67–7.63 (m, 2H), 7.44–7.38 (m, 2H), 7.35–7.29 (m, 1H), 6.91–6.86 (m, 1H), 6.69 (s, 1H), 6.60–6.58 (m, 2H), 6.46–6.39 (m, 3H), 4.46 (q, $J = 6.7$, 1H), 3.41 (ddd, $J = 13.2$, 9.3 and 3.7, 1H), 3.22–3.09 (m, 4H), 3.07–2.91 (m, 3H), 1.32 (d, $J = 6.7$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 141.1, 140.5, 139.6, 139.1, 136.4, 136.2, 135.4, 133.3, 132.8, 132.6, 132.45, 132.40, 132.2, 130.1, 129.2, 127.3, 45.1, 35.6, 35.35, 35.30, 33.1, 25.3. IR (cm^{-1}): ν : 731, 860, 907, 1057, 1368, 1441, 1437, 1478, 1583, 2852, 2923, 3007. HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{24}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 367.1496; found, 367.1508.

4-[1'-(tert-Butylsulfanyl)ethyl]-[2.2]paracyclophane (4b). The compound was obtained following the general procedure from ketone **3** (125 mg, 0.5 mmol), *t*-butanethiol ($\text{R}^1 = t\text{-Bu}$, 62 μL , 0.55 mmol), trifluoroacetic acid (193 μL , 2.5 mmol, 5 equiv), and $\text{BH}_3\cdot\text{THF}$ (1 M solution, 550 μL , 0.55 mmol) in CH_2Cl_2 (2 mL) as a mixture (85:15 ratio) of diastereoisomers. Yield: 79% (128 mg, 0.395 mmol). Separation was achieved by column chromatography on silica gel (pentane/ CH_2Cl_2 , 4:1). (S_p,R)*-**4b** (major diastereoisomer). White solid. Mp: 117–118 °C. TLC (pentane/ CH_2Cl_2 , 4:1) $R_f = 0.64$. ^1H NMR (400 MHz, CDCl_3): δ 6.60–6.53 (m, 3H), 6.45–6.36 (m, 4H), 4.11 (q, $J = 6.9$, 1H), 3.60–3.51 (m, 1H), 3.25–2.89 (m, 7H), 1.84 (d, $J = 6.9$, 3H), 1.33 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 141.5, 139.9, 139.7, 139.4, 137.0, 135.6, 133.4, 132.9, 132.1, 131.9, 130.3, 130.1, 43.9, 38.8, 35.5, 35.3, 35.1, 33.6, 31.9, 22.5. IR (cm^{-1}): ν : 750, 764, 794, 860, 1161, 1260, 1275, 1370, 1457, 1593, 2854, 2895, 2924, 3006. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{28}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 347.1809; found, 347.1812. (S_p,S)*-**4b** (minor diastereoisomer). White solid. Mp: 109–110 °C. TLC (pentane/ CH_2Cl_2 , 4:1) $R_f = 0.84$. ^1H NMR (400 MHz, CDCl_3): δ 6.95 (d, $J = 7.8$, 1H), 6.63–6.55 (m, 2H), 6.50 (s, 1H), 6.43 (d, $J = 7.8$, 1H), 6.35–6.29 (m, 2H), 4.09 (q, $J = 6.8$, 1H), 3.44–3.35 (m, 1H), 3.23–3.03 (m, 4H), 3.00–2.86 (m, 3H), 1.54 (s, 9H), 1.45 (d, $J = 6.8$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 142.8, 140.2, 139.6, 139.0, 135.35, 135.30, 133.5, 132.6, 132.5, 132.1, 131.8, 130.1, 43.8, 38.6, 35.5, 35.25, 35.20, 33.0, 32.3, 29.1. IR (cm^{-1}): ν : 750, 764, 1055, 1159, 1261, 1275, 1363, 1457, 1592, 2854, 2924. HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{28}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 347.1809; found, 347.1804.

4-[1'-(Isopropylsulfanyl)ethyl]-[2.2]paracyclophane (4c). The compound was obtained following the general procedure from ketone **3** (125 mg, 0.5 mmol), isopropanethiol ($\text{R}^1 = i\text{-Pr}$, 52 μL , 0.55 mmol), trifluoroacetic acid (193 μL , 2.5 mmol, 5 equiv), and $\text{BH}_3\cdot\text{THF}$ (1 M solution, 550 μL , 0.55 mmol) in CH_2Cl_2 (2 mL) as a mixture (86:14 ratio) of diastereoisomers. Yield: 85% (131 mg, 0.425 mmol). Separation was achieved by column chromatography on silica gel (pentane/ CH_2Cl_2 , 4:1). (S_p,R)*-**4c** (major diastereoisomer). White

solid. Mp: 128–129 °C. TLC (pentane/ CH_2Cl_2 , 4:1) $R_f = 0.62$. ^1H NMR (400 MHz, CDCl_3): δ 6.56–6.50 (m, 3H), 6.46–6.37 (m, 4H), 4.04 (q, $J = 6.8$, 1H), 3.64–3.55 (m, 1H), 3.24–2.86 (m, 7H), 2.78 (sept, $J = 6.7$, 1H), 1.75 (d, $J = 6.8$, 3H), 1.27 (d, $J = 6.7$, 3H), 1.12 (d, $J = 6.7$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 140.6, 140.0, 139.7, 139.5, 137.8, 135.5, 133.6, 133.0, 132.1, 131.8, 130.0, 129.9, 39.0, 35.5, 35.4, 34.9, 33.7 (2 signals overlapping), 23.8, 23.6, 19.7. IR (cm^{-1}): ν : 750, 764, 861, 1260, 1275, 1452, 1592, 2854, 2925, 2954, 3007. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{26}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 333.1653; found, 333.1652. (S_p,S)*-**4c** (minor diastereoisomer). White solid. Mp: 62–63 °C. TLC (pentane/ CH_2Cl_2 , 4:1) $R_f = 0.82$. ^1H NMR (400 MHz, CDCl_3): δ 6.88 (d, $J = 7.9$, 1H), 6.60–6.52 (m, 3H), 6.47 (d, $J = 7.9$, 1H), 6.39–6.33 (m, 2H), 4.07 (q, $J = 6.8$, 1H), 3.43–3.32 (m, 1H), 3.21–2.86 (m, 8H), 1.51 (d, $J = 6.4$, 3H), 1.42 (d, $J = 6.8$, 3H), 1.37 (d, $J = 6.8$, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 142.1, 140.3, 139.6, 139.1, 136.1, 135.3, 133.3, 132.8, 132.5, 132.2, 131.8, 130.3, 39.6, 35.5, 35.3, 35.2, 34.2, 33.2, 25.5, 23.9, 23.8. IR (cm^{-1}): ν : 750, 764, 1049, 1260, 1275, 1454, 1593, 2854, 2924, 2956, 3006. HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{26}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 333.1653; found, 333.1667.

Transformation of Sulfanyl Ester 2e. 4-(Methylsulfanyl)-methyl[2.2]paracyclophane (2f). In a two-necked round-bottomed flask, equipped with a nitrogen inlet, sulfanyl ester **2e** (194.7 mg, 0.57 mmol, 1 equiv) was diluted in dry THF (3 mL). After cooling to -78 °C, *t*-BuOK (686 μL of a 1 M solution in THF, 1.2 equiv) was added dropwise. The reaction was stirred at -78 °C for 30 min, and iodomethane (39 μL , 0.63 mmol, 1.1 equiv) was added. After additional stirring for 20 min at -78 °C, water was added, and the reaction mixture was allowed to warm to room temperature. Volatiles were removed under reduced pressure, and the aqueous phase was extracted twice with CH_2Cl_2 . The collected organic layers were dried over MgSO_4 and concentrated under a vacuum. The resulting crude product was then purified by column chromatography on silica gel (pentane/ CH_2Cl_2 , 70:30) to afford the expected sulfide **2f**. Yield: 79% (120.5 mg, 0.45 mmol). White solid. Mp: 83–84 °C. TLC (pentane/ CH_2Cl_2 , 70:30) $R_f = 0.32$. ^1H NMR (400 MHz, CDCl_3): δ 6.67 (dd, $J = 7.9$ and 1.7, 1H), 6.56–6.45 (m, 4H), 6.43 (dd, $J = 7.8$ and 1.7, 1H), 6.27 (s, 1H), 3.71 (d, $J = 13.4$, 1H), 3.50–3.41 (m, 1H), 3.35 (d, $J = 13.4$, 1H), 3.23–3.14 (m, 1H), 3.13–2.95 (m, 5H), 2.87 (ddd, $J = 13.6$, 10.8 and 6.2, 1H), 1.92 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 139.9, 139.6, 139.4, 137.9, 137.4, 135.25, 135.20, 133.5, 133.3, 132.2, 131.6, 129.0, 37.1, 35.4, 35.0, 34.4, 33.4, 15.1. IR (cm^{-1}): ν : 716, 753, 795, 868, 906, 1237, 1411, 1426, 1592, 2850, 2924, 3006, 3030. HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{20}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 291.1183; found, 291.1194. Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{S}$: C, 80.55; H, 7.51; S, 11.94. Found: C, 80.24; H, 7.51; S, 12.28.

[(2.2)Paracyclophan-4-yl]methanethiol ((±)-5). In a two-necked round-bottomed flask, sulfanyl ester ((±)-**2e**) (345.5 mg, 1.01 mmol, 1 equiv) was diluted in dry THF (5 mL). After cooling to -78 °C, *t*-BuOK (2 mL of a 1 M solution in THF, 2 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 30 min and then directly poured onto an aqueous 1 M HCl solution (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 \times 20 mL), and the collected organic layers were dried over MgSO_4 and concentrated under a vacuum. The resulting crude product was then purified by column chromatography on silica gel (pentane/ CH_2Cl_2 , 80:20) to afford the expected thiol ((±)-**5**). Yield: 80% (204.2 mg, 0.80 mmol). White solid. Mp: 143–144 °C. TLC (pentane/ CH_2Cl_2 , 80:20) $R_f = 0.22$. ^1H NMR (400 MHz, CDCl_3): δ 6.63 (dd, $J = 7.8$ and 1.8, 1H), 6.53–6.44 (m, 4H), 6.41 (dd, $J = 7.8$ and 1.8, 1H), 6.30 (s, 1H), 3.73 (dd, $J = 13.1$ and 7.2, 1H), 3.49–3.38 (m, 2H), 3.23–3.13 (m, 1H), 3.12–2.94 (m, 5H), 2.93–2.82 (ddd, $J = 13.6$, 10.8 and 6.1, 1H), 1.54 (t, $J = 7.2$, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 140.5, 140.3, 139.7, 139.4, 137.1, 135.5, 134.1, 133.6, 133.4, 132.3, 131.8, 128.9, 35.4, 35.1, 34.5, 33.3, 27.8. IR (cm^{-1}): ν : 638, 794, 871, 1239, 1412, 1497, 1591, 2539, 2849, 2924. HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{18}\text{NaS}$ [$\text{M} + \text{Na}$] $^+$, 277.1027; found, 277.1026. Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{S}$: C, 80.27; H, 7.13; S, 12.60. Found: C, 79.81; H, 7.31; S, 12.22.

Resolution Protocol of Sulfanyl Ester ((±)-2e) by Semi-preparative HPLC. The racemic sulfanyl ester ((±)-**2e**) (1.50 g, 4.41

mmol) was dissolved in the minimum amount of a 60:40 *n*-heptane/ethanol mixture. Aliquots of the resulting solution were repeatedly injected into the semipreparative HPLC apparatus equipped with an IA column (5 μ m; size = 250 mm \times 20 mm) eluting with 60:40 *n*-heptane/ethanol at 1 mL min⁻¹ (20 °C) and with UV monitoring at 229 nm. The collected fractions of each enantiomer, eluted at 5.96 and 17.91 min, were concentrated *in vacuo*. Individual fractions of enantiomers thus isolated were reinjected onto an analytical chiral IA column (5 μ m; size 250 mm \times 4.6 mm) to determine their enantiomeric purity. The absolute configuration within (–)-**2e** and (+)-**2e** was unambiguously assigned by chemical correlation to the related thiols (*vide infra*).

(*R_p*)-(–)-**2e** was the first-eluted fraction in a total yield of 596 mg (1.75 mmol, 100% ee). HPLC: *t_R* = 5.96 min (IA column (5 μ m; size = 250 mm \times 4.6 mm); flow rate = 1.0 mL min⁻¹; *n*-heptane/ethanol 60:40; 20 °C, 229 nm). [α]_D²⁰ –14.2 (c 0.01, CHCl₃). Other spectral data are similar to those previously given for the racemic sample.

(*S_p*)-(+)-**2e** was the second-eluted fraction in a total yield of 613 mg (1.80 mmol, 100% ee). HPLC: *t_R* = 17.91 min (IA column (5 μ m; size = 250 mm \times 4.6 mm); flow rate = 1.0 mL min⁻¹; *n*-heptane/ethanol 60:40; 20 °C, 229 nm). [α]_D²⁰ +13.9 (c 0.01, CHCl₃). Other spectral data are similar to those previously given for the racemic sample.

Deprotection into Enantiopure Thiols 5. The deprotection was carried out as described before with the racemic material, and the configuration of both enantiomers was unambiguously assigned by X-ray crystallography.

(*R_p*)-(–)-**5** was obtained from sulfanyl ester (*R_p*)-(–)-**2e**. Yield: 79% (50.2 mg, 0.197 mmol, 100% ee). White solid. Mp: 143–144 °C. Spectral data are similar to those previously given for the racemic sample. HPLC: *t_R* = 4.72 min (IA column (5 μ m; size = 250 mm \times 4.6 mm); flow rate = 1.0 mL min⁻¹; *n*-heptane/EtOH 80:20; 20 °C, 210 nm). [α]_D²⁰ –37.6 (c 0.01, CHCl₃).

(*S_p*)-(+)-**5** was obtained from sulfanyl ester (*S_p*)-(+)-**2e**. Yield: 76% (48.2 mg, 0.189 mmol, 100% ee). White solid. Mp: 143–144 °C. Spectral data are similar to those previously given for the racemic sample. HPLC: *t_R* = 6.38 min (IA column (5 μ m; size = 250 mm \times 4.6 mm); flow rate = 1.0 mL min⁻¹; *n*-heptane/EtOH 80:20; 20 °C, 210 nm). [α]_D²⁰ +36.3 (c 0.01, CHCl₃).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.0c02235>.

Optimization of the reaction conditions; stereochemical assignment; transition state model; cross-experiments; chemoselectivity, crystallographic data for **2a**, **4a**, and (*R_p*)-**5**; HPLC chromatographs; NMR spectra for all new products (PDF)

Accession Codes

CCDC 1909740–1909742 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from ERDF funding (ISCE-Chem & INTERREG IVa program), CNRS, and Synorg Labex (ANR-11-LABX-0029). We thank Julien Del Corpo and Romain Saubion (ENSICAEN) for contributing to the optimization of the protocols.

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