Towards a Flexible Strategy for the Synthesis of Enantiomerically Pure [2.2]Paracyclophane Derivatives: The Chemistry of 4-Tolylsulfinyl[2.2]paracyclophane

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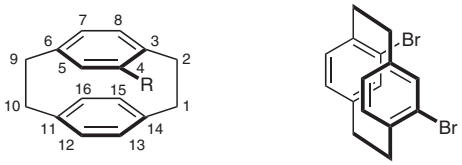
Abstract: The use of enantiomerically enriched 4-tolylsulfinyl[2.2]paracyclophane as a precursor to a variety of mono- and disubstituted [2.2]paracyclophane derivatives is described. The goal of our research is to develop a single general precursor that permits the synthesis of the most common [2.2]paracyclophane substitution patterns. The chemistry of two diastereoisomers of 4-tolylsulfinyl[2.2]paracyclophane has been explored and it facilitates the synthesis of enantiomerically enriched 4-substituted and 4,13-disubstituted [2.2]paracyclophanes. Directed lithiations result in an unusual cyclisation reaction. Whilst the tolyl group cannot realise our goal, the chemistry outlined acts as a successful 'proof of concept.'

Key words: asymmetric synthesis, cyclophanes, sulfoxides, enantiomeric resolution

[2.2]Paracyclophane (**1a**; R = H, Figure 1) was first prepared by Brown 60 years ago,[1] but it was the pioneering studies of Cram that initiated the field of paracyclophane chemistry.[2] The popularity of [2.2]paracyclophane, which has seen it become one of the most studied hydrocarbons, arises from its unique structural, physical, and electronic properties.[3]



1a R = H
1b R = CHO
1c R = CO_2H
1d R = OH
1e R = NH_2
1f R = COMe
1g R = Br
1h R = Me
1i R = $SiMe_3$
1j R = $P(O)Ph_2$
1k R = D
2

Figure 1 Common [2.2]paracyclophane derivatives

It was recognised as early as 1955 that appropriately substituted [2.2]paracyclophane derivatives exhibited planar chirality,[4] yet no applications in stereoselective synthesis were reported until the early 1990s.[5,6] Since that time, enantiomerically pure [2.2]paracyclophane compounds have been employed with varying degrees of success in all aspects of asymmetric synthesis. It is clear that [2.2]paracyclophane-derived compounds show great potential in asymmetric synthesis, yet compared to planar chiral ferrocenyl derivatives or η^6-arene transition-metal complexes there is a paucity of reports and the field is still in its relative infancy. Arguably, the most significant impediment to expanding this area is the lack of attractive strategies for the preparation of enantiomerically enriched [2.2]paracyclophane derivatives;[5,7] the field is still dominated by tedious and frequently expensive resolution protocols. This shortcoming arises as the introduction of just one substituent breaks the symmetry of [2.2]paracyclophane, and, therefore, needs to be enantioselective. In ferrocenyl and η^6-arene complexes two substituents are required to establish planar chirality, thus allowing the first substituent to be used to control the enantioselective introduction of the second.[8]

In this paper we report the full details of our first steps towards a general strategy for the formation of enantiomerically enriched [2.2]paracyclophane derivatives from a common precursor. Parts of this chemistry have previously been reported.[9,10]

Currently, enantiomerically enriched [2.2]paracyclophane compounds are either resolved on an ad hoc basis[11] or are derived from one of the key precursors **1b–f** and **2** (Figure 1). The optimum routes to these enantiomerically enriched compounds appear to be; aldehyde **1b** via multiple recrystallisations of Schiff base derviatives[12] or enzymatic methods;[13] carboxylic acid **1c** by recrystallisation of diastereoisomeric salts;[14] phenol **1d** by esterification with a chiral acid chloride,[15] enzymatic resolution of the acetate;[16] amine **1e** by multiple recrystallisations of diastereoisomeric salts;[17] methyl ketone **1f** via HPLC[18] or diastereoisomeric hydrazone derivatives.[19] Resolved 4-bromo[2.2]paracyclophane (**1g**) is now available via a kinetic resolution-amination protocol.[20] 4,12-Disubstituted [2.2]paracyclophane derivatives are invariably prepared from 4,12-dibromo[2.2]paracyclophane **2**, which can be obtained by kinetic resolution utilising the Buchwald–Hartwig amination protocol[21] or by chiral HPLC.

We were interested in developing a methodology that will permit the synthesis of any of the common [2.2]paracyclophane substitution patterns **4–7** in enantiomerically enriched form from a common precursor **3** (Scheme 1). Of all the possible chiral directing groups, the sulfoxide moiety offers sufficient versatility to fulfil all these criteria.

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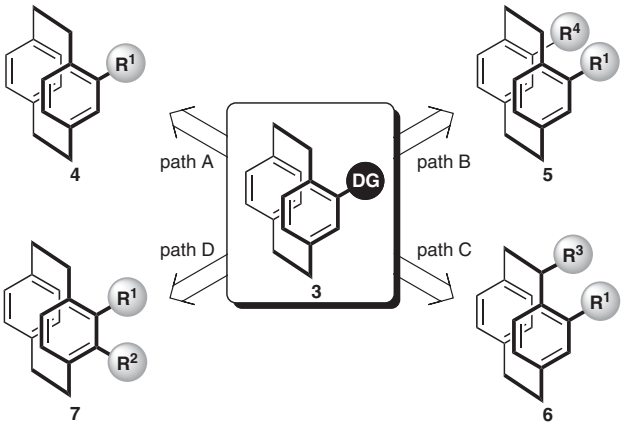
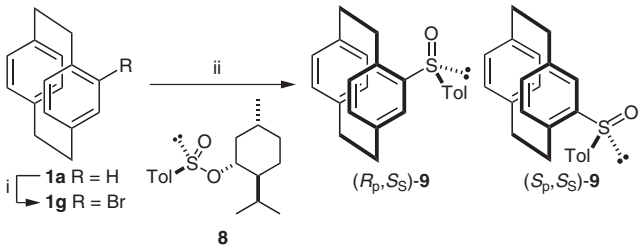
Due to the commercial availability of the Andersen reagent, (1*R*,2*S*,5*R*)-(–)-menthyl (*S*)-*p*-toluenesulfinate (**8**), and its diastereoisomers, as well as a previous report by Reich and Yelm[22] employing the tolylsulfinyl moiety to resolve [2.2]paracyclophanes, we began investigating the chemistry of 4-tolylsulfinyl[2.2]paracyclophane (**9**).



Scheme 1 General strategy for the synthesis of enantiomerically pure [2.2]paracyclophane derivatives from a common precursor

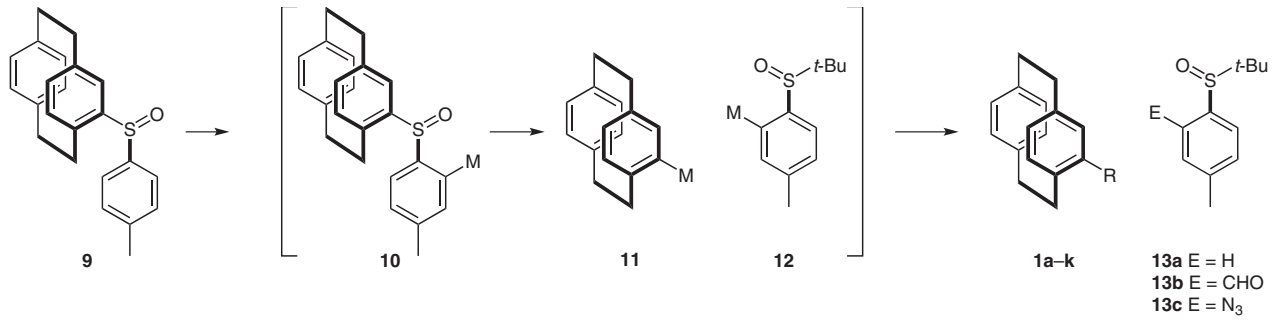
The sulfoxide moiety must meet two criteria: it must allow simple resolution and it must undergo direct substitution; other auxiliaries have been employed to resolve the planar chirality of [2.2]paracyclophane, but all have been retained in the final product or have required several steps to remove.[23,24] Therefore, the first goal was the synthesis of enantiopure 4-monosubstituted [2.2]paracyclophane derivatives **4**. Treatment of racemic 4-bromo[2.2]paracyclophane (**1g**)[25] with *n*-BuLi followed by Andersen reagent **8** permitted stereospecific sulfination and the formation of a 1:1 mixture of diastereoisomers (R_p,S_S)-**9** and (S_p,S_S)-**9** in good yield (Scheme 2). The two diastereoisomers were readily separated utilising gradient elution column chromatography; the [2.2]paracyclophane contaminate is removed first before elution of (R_p,S_S)-**9** followed by (S_p,S_S)-**9**. Separation has been achieved on a 10 g scale without issue. As nucleophilic substitution of sulfinates proceeds with inversion at sulfur, the two diastereoisomers differ only by their planar chirality. This chemistry is equally effective with the diastereoisomer of **8**, (1*R*,2*S*,5*R*)-(–)-menthyl (*R*)-*p*-toluenesulfinate, which gives a 1:1 mixture of (S_p,R_S)-**9** and (R_p,R_S)-**9** in 50% yield.



Scheme 2 Resolution of planar chirality. *Reagents and conditions*: i. Br_2/Fe, CH_2Cl_2, >99%; ii. (a) *n*-BuLi (1.05 equiv), THF, –78 °C, (b) **8**, THF, 61%.

Both diastereoisomers are highly crystalline and we were able to confirm Reich and Yelm's original assignment of the relative stereochemistry, which was based on derivatisation,[22] by X-ray crystallography.[9,26] As highlighted in the original synthesis, the ^{1}H NMR shifts are highly indicative of the orientation of the sulfinyl oxygen. In the (R_p,S_S)-**9** diastereoisomer, the oxygen is directed towards the bridgehead methylene group and the anisotropic influence of the sulfoxide causes $H2_{syn}$ to be deshielded in comparison to the other diastereoisomer [3.84 ppm versus 3.50 ppm in (S_p,S_S)-**9**]. In diastereoisomer (S_p,S_S)-**9**, the sulfinyl oxygen is orientated towards the *ortho* hydrogen, H5, resulting in this hydrogen displaying a downfield resonance of 7.13 versus 6.58 ppm in (R_p,S_S)-**9**.[26]

Having resolved the planar chirality, substitution of the sulfinyl moiety was investigated (Path A; Scheme 1). In order to access an extensive range of products, sulfoxide–metal exchange to give an enantiomerically enriched 4-metallo[2.2]paracyclophane **11** was investigated. Disappointingly, application of Reich and Yelm's methodology, employing *n*-BuLi followed by excess DMF gave only a trace of product **1b** along with [2.2]paracyclophane **1a** (Scheme 3; Table 1, entry 1,). Clearly, sulfoxide–metal exchange had occurred, but protonation was faster than addition. Deeming that a soft 4-metallo[2.2]paracyclophane **11** would be less basic, we utilised the conditions of Satoh et al.[27] to convert the sulfoxide into a cuprate via the intermediacy of a Grignard reagent, then reacted it with MeI to give 4-methyl[2.2]paracyclophane (**1h**) and starting material (Table 1, entry 2). Omitting the copper salt from this reaction gave comparable results (Table 1,



Scheme 3 Formation of 4-monosubstituted [2.2]paracyclophane derivatives and the possible mechanism. *Reagents and conditions*: see Tables 1 and 2.

entry 3). When a less reactive electrophile was employed, namely DMF, only **1a** and unreacted starting material **9** was recovered (Table 1, entry 4). Using a large excess of EtMgBr resulted in the consumption of more **9** but failed to yield any product (Table 1, entry 5). 4-Metallo[2.2]paracyclophanes formed by halogen–metal exchange are known to react efficiently, therefore, the isolation of **1a** implicates the ethylsulfoxide by-product as the source of protons that inhibits reaction. Employing *tert*-butyl organometallic reagents removes the relatively acidic α-protons thus avoiding premature protonation. Use of *t*-BuMgBr provided unsatisfactory results (Table 1, entry 6), but *t*-BuLi proved more encouraging; all starting material was rapidly consumed and, on addition of iodomethane, **1h** was produced (30%) along with **1a** (40%) and *tert*-butylsulfinyl-*p*-toluene (**13a**) (16%; Table 1, entry 7). More auspiciously reaction with DMF gave aldehyde **1b** in good yield (62%; Table 1, entry 8) along with **1a**, **13a**, and 2-(*tert*-butylsulfinyl)-5-methylbenzaldehyde (**13b**) (Scheme 3). Performing the reaction at a higher temperature accelerates the detrimental side reactions (Table 1, entries 9 and 10). Extensive optimisation led to conditions that minimised the formation of [2.2]paracyclophane **1a** (Table 1, entry 11).

The scope of the reaction was then ascertained by varying the electrophile (Table 2). Pleasingly, the methodology permits the synthesis of four key enantiomerically enriched monosubstituted [2.2]paracyclophane precursors **1b–e** in comparable or improved yields to previous resolutions (Table 2, entries 1–4,). Whilst, the yield of **1e** was not ideal (32% for two steps), the reaction could be performed on both a 0.3 mmol (100 mg) and a 3.0 mmol (1 g) scale without loss in yield. The methodology also permitted the first reported preparation of the phosphine oxide **1j** in enantiomerically pure form (Table 2, entries 7 and 8);[28] presumably, aerial oxidation occurs on purification in the latter reaction.

Other electrophiles, such as iodine, bromine, and acetyl chloride gave only [2.2]paracyclophane. Considering all these reagents react with 4-lithio[2.2]paracyclophane generated from 4-bromo[2.2]paracyclophane, it is fair to assume that the basic nature of [2.2]paracyclophane in conjunction with the formation of a comparatively acidic

Table 2 Synthesis of Enantiomerically Enriched Monosubstituted [2.2]Paracyclophanes (Scheme 3)

Entry	Electrophile	Product	R	Yield (%)	Yield (%) of resolution[a]
1	DMF	**1b**	CHO	81	25 (20)[13]
2	$CO_{2(s)}$	**1c**	CO_2H	77	24 (24)[14]
3	$B(OMe)_3$	**1d**	OH	53[b]	16 (11)[15]
4	TsN_3	**1e**	NH_2	32[c]	10[c] (24)[17]
5	MeI	**1h**	Me	64	–
3	TMSCl	**1i**	TMS	44	–
6	$Ph_2P(O)Cl$	**1j**	$P(O)Ph_2$	52	–
7	Ph_2PCl	**1j**	$P(O)Ph_2$	90[d]	–
8	D_2O	**1k**	D	48	–

[a] Overall yield from racemic (±)-4-bromo[2.2]paracyclophane to one enantiomer of product. Literature yield is given in parentheses.
[b] Boron adduct was not isolated, but oxidised in situ with NMO.
[c] The low yield is due to a problematic reduction of 4-azido[2.2]paracyclophane, which occurs in only 40%.
[d] Phosphine is believed to oxidise on purification.

Table 1 Optimisation for the Formation of 4-Monosubstituted [2.2]Paracyclophane Derivatives from **9**

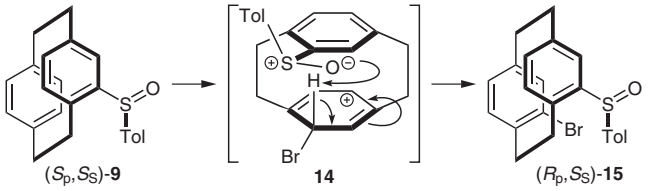
Entry	R^1M (equiv)	RX (equiv)	Product	Yield (%)	**9** (%)	**1a** (%)	Others[a] (%)
1	*n*-BuLi (6.0)	DMF (12.0)	**1b**	<5	0	>95	–
2	EtMgBr (3.5), CuBr (0.5)	MeI (4.0)	**1h**	61	36	–	–
3	EtMgBr (3.5)	MeI (4.0)	**1h**	62	36	0	–
4	EtMgBr (3.5)	DMF (4.0)	–	0	52	44	–
5	EtMgBr (9.0)	DMF (12.0)	–	0	10	66	–
6	*t*-BuMgBr (2.0)	MeI (4.0)	–	0	53	–	–
7	*t*-BuLi (2.0)	MeI (4.0)	**1h**	30	0	40	16 (**13a**)
8	*t*-BuLi (2.0)	DMF (4.0)	**1b**	62	0	27	15 (**13a**), 29 (**13b**)
9[b]	*t*-BuLi (2.0)	DMF (4.0)	–	0	0	80	–
10[b]	*t*-BuLi (3.0)	DMF (6.0)	**1b**	16	0	45	15 (**13a**), 21 (**13b**)
11	*t*-BuLi (4.0)	DMF (8.0)	**1b**	81	0	18	–
12	*t*-BuLi (4.0)	TsN_3 (8.0)	**1e**	32[c]	0	54	13 (**13a**), 20 (**13c**)

[a] See Scheme 3.
[b] Reaction performed at 0 °C.
[c] Yield is for two steps; azide formation and reduction with $NaBH_4$.

sulfoxide by-product is the source of these disappointing results.

We believe that the substitution reaction is not as simple as it appears. Up to four products **1b–k**, **1a**, **13a** and **13b**, or **13c** (Scheme 3) can be isolated from these reactions and this suggests the following: It is unlikely that direct substitution of the [2.2]paracyclophanyl moiety by the *tert*-butyl group occurs. Due to its high basicity, [2.2]paracyclophane is a less effective leaving group than *p*-tolyllithium. The high basicity of 4-lithio[2.2]paracyclophane is apparent in the reaction of **11** (M = Li) with MeI, which gives up to 34% yield of 4-iodo[2.2]paracyclophane along with the expected 4-methyl[2.2]paracyclophane. A similar result was observed by Cram.[29] The iodide arises due to a second metal–halogen exchange. Equally improbable is the sequential displacement of *p*-tolyllithium, to give 4-*tert*-butylsulfinyl[2.2]paracyclophane, followed by a second substitution to give **11** and di-*tert*-butyl sulfoxide; we have shown that 4-*tert*-butylsulfinyl[2.2]paracyclophane does not participate in sulfoxide–metal exchange reactions.[30] Therefore, we posit that *ortho*-lithiation of the tolyl moiety to give **10** occurs prior to displacement by *t*-BuLi. Compounds **1b–j** and **13a–c** are formed by reaction of **11** and **12** with an electrophile. [2.2]Paracyclophane **1a** arises as **11** competes with *t*-BuLi to form **10**.

The most striking feature of the results in Table 2 is not that the sulfoxide methodology compares favourably with the known resolution strategies (entries 1 to 4), but that all these compounds can be prepared in enantiomerically pure form from the same precursor. Whilst this methodology is still a resolution, it is a significant advance due to its versatility.



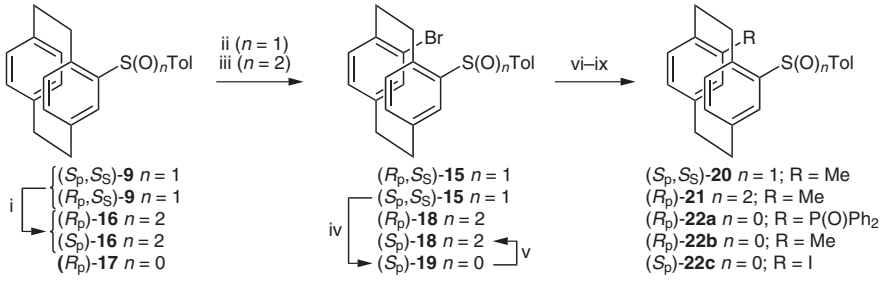
Scheme 4 *Pseudo-gem* directed functionalisation. *Reagents and conditions*: Fe/Br_2, CH_2Cl_2, 57%.

Having proven the feasibility of employing the sulfoxide moiety as a 'traceless' resolving group, we turned our attention to the synthesis of disubstituted derivatives.

The simplest disubstituted [2.2]paracyclophane derivatives to prepare are the *pseudo-gem* [2.2]paracyclophanes **5** (Scheme 1). The *pseudo-gem* effect directs electrophilic aromatic substitution reactions to the thermodynamically disfavoured position directly opposite the original substituent. The basis of this effect is the formation of a σ-complex in which the *pseudo-gem* hydrogen atom (H13) is orientated towards a basic atom on the 4-substituent (e.g., **14**; Scheme 4).[31,32] This alignment facilitates an intramolecular proton transfer step and promotes deprotonation.

Our plan was to direct bromination to the C13 position and then employ halogen–metal exchange to introduce a range of electrophiles. Reich and Yelm have shown that the sulfone moiety could direct bromination[22] but sulfoxides have never been employed in this reaction. We were conscious that the reactivity of the sulfoxide group could compromise chemoselectivity in the subsequent halogen–exchange reaction, and therefore, the bromosulfone analogue **18** and the bromosulfide **19** were also prepared (Scheme 5).

Treatment of (S_p,S_S)-**9** with iron and bromine furnished the desired *pseudo-gem*-disubstituted [2.2]paracyclophane (R_p,S_S)-**15** in moderate yield (57%) along with unreacted starting material. More starting material could be consumed, but at the detriment of the yield as more side-products were formed. Reaction of diastereoisomer (R_p,S_S)-**9** was less successful, giving only 35% of the desired bromide (S_p,S_S)-**15** before deoxygenation, and subsequent nonselective bromination, became an issue. Presumably, interaction between the ethylene bridge and the tolyl moiety hinders rotation and the molecule cannot adopt the correct conformation for efficient intramolecular hydrogen transfer; this unfavourable conformation can be inferred by comparing the X-ray crystallographic structures of bromides (S_p,S_S)-**15** and (R_p,S_S)-**15** (Figure 2). In (S_p,S_S)-**15** the sulfinyl oxygen is orientated away from the lower ring whilst in (R_p,S_S)-**15** there is less hindrance to it approaching the lower ring.



Scheme 5 Synthesis of *pseudo-gem* disubstituted [2.2]paracyclophane derivatives. *Reagents and conditions*: i. *m*-CPBA, CH_2Cl_2 [(R_p)-**16** 61%; (S_p)-**16** >98%]; ii. Br_2/Fe, CH_2Cl_2 [(S_p,S_S)-**9** → (R_p,S_S)-**15** 57%; (R_p,S_S)-**9** → (S_p,S_S)-**15** 35%]; iii. Br_2/Fe, CCl_4 [(S_p)-**16** → (R_p)-**18** 61%]; iv. $HSiCl_3$, Et_3N, THF, reflux [(S_p,S_S)-**15** → (S_p)-**19** 98%]; v. *m*-CPBA, CH_2Cl_2 [(S_p,S_S)-**19** → (S_p)-**18** 28%]; vi. (a) *i*-$PrBu_2MgLi$, THF, 0 °C, (b) MeI, THF, 0 °C [(R_p,S_S)-**15** → (S_p,S_S)-**20** 48%]; vii. (a) *n*-BuLi, THF, –78 °C, (b) MeI, THF, 0 °C [(S_p)-**18** → (R_p)-**21** 40%]; viii. (a) *i*-$PrBu_2MgLi$, THF, 0 °C, (b) $Ph_2P(O)Cl$, THF, 0 °C [(S_p)-**19** → (R_p)-**22a** 88%]; ix. (a) *t*-BuLi, THF, –78 °C, (b) MeI, THF, –78 °C [(S_p)-**19** → (R_p)-**17** 55%, (R_p)-**22b** 34%, (S_p)-**22c** 11%].

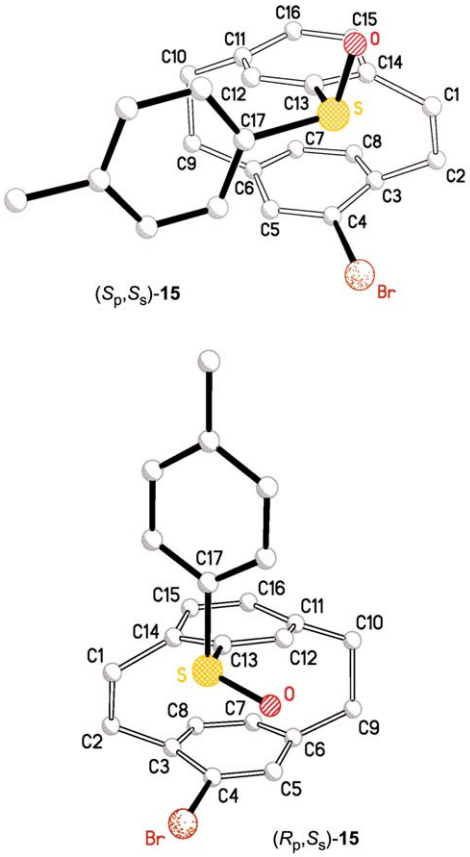


Figure 2 X-ray crystal structure of *pseudo-gem* brominated sulfoxides (S_p,S_S)-**15** and (R_p,S_S)-**15**[26b]

The side-products arise from the reduction of the sulfoxide to an electron-donating sulfide, which promotes non-selective bromination. The major side-product involves bromination of the electron rich upper ring *para* to the sulfinyl moiety. Dibromination of the [2.2]paracyclophane moiety deactivates it, and subsequent bromination occurs in the *ortho* position of the tolyl ring. The structures were inferred from X-ray crystallography studies.[33]

The bromosulfone (R_p)-**18** was synthesised according to the literature[22] whilst its enantiomer, (S_p)-**18**, was prepared by the oxidation of bromosulfide (S_p,S_S)-**19**. The sulfide (S_p)-**19** was prepared by the reduction of (S_p,S_S)-**15** with $HSiCl_3$ and Et_3N at reflux (Scheme 5).[34]

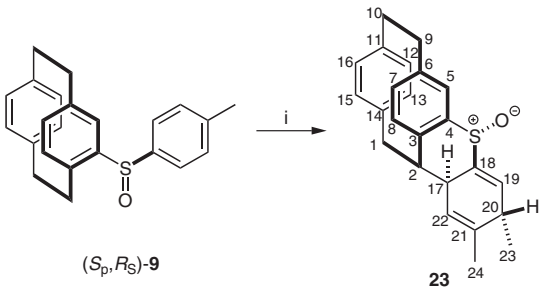
Treatment of sulfoxide (R_p,S_S)-**15** with *n*-BuLi followed by MeI led to a complex mixture of products comprised of predominantly [2.2]paracyclophane **1a** and only 8% of the desired (S_p,S_S)-**20** (Scheme 5). It was clear that nonselective metal exchange was occurring. After screening various conditions, the most selective halogen–metal exchange was achieved with Oshima's magnesate, lithiumdibutylisopropylmagnesate (*i*-PrBu$_2$MgLi).[35] Addition of (R_p,S_S)-**15** to a solution of *i*-PrBu$_2$MgLi at 0 °C followed by the addition of MeI gave (S_p,S_S)-**20** in an improved 48% yield along with **1a** (40%).

Neither the sulfone **18** nor the sulfide **19** completely ameliorated the low yields. Whilst selective halogen–metal exchange was possible in both cases, other issues affected the efficiency. Reaction of the electron-rich sulfide (S_p)-**19** was highly capricious, with additions to diphenylphosphoryl chloride furnishing phosphine oxide (R_p)-**22a** with yields varying from 10–88% (Scheme 5). Use of other electrophiles invariably resulted in protonation and formation of sulfide (R_p)-**17**. The sulfide moiety detrimentally increases the basicity of the system, as highlighted by the reaction of (S_p)-**19** with *t*-BuLi and MeI. In addition to the formation of methyl derivative (R_p)-**22b** (34%) and sulfide (R_p)-**17** (38%), the iodide (S_p)-**22c** (11%) was also observed. The electron-deficient bromosulfone (S_p)-**18** was no less idiosyncratic, furnishing both the desired methylated (R_p)-**21** (40% yield) and considerable amounts of proto-debrominated (R_p)-**16**. Additionally, the NMR spectra indicated that the sulfone had directed lithiation to the *ortho* position on the tolyl moiety.

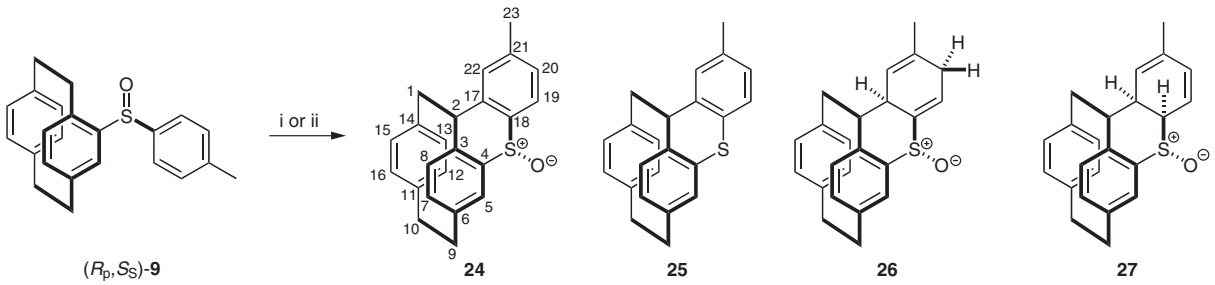
The current results serve as a 'proof of concept'; it is possible to use the sulfoxide moiety to direct functionalisation to the second ring of [2.2]paracyclophane. The tolylsulfinyl group is capable of directing *pseudo-gem* bromination, but it is too reactive to permit selective metal exchange. Conversion to more robust functionality, either the sulfide or the sulfone alleviates the problem of selective exchange, but both are still hampered by side reactions.

Sulfoxides are known to be excellent auxiliaries for directed metallations[36] and we were interested in applying this chemistry to further functionalise the [2.2]paracyclophane backbone. The issue of regioselectivity prevented directed *ortho*-metallation at C5 of diastereoisomer (S_p,S_S)-**9**. García Ruano et al. have reported high chemoselectivity in sulfoxide-directed metallations of benzylic methylenes in preference to *ortho*-metallation[37] and we believed that employing their methodology with diastereoisomer (R_p,S_S)-**9** or (S_p,R_S)-**9**, in which the sulfinyl oxygen is orientated towards C2, would permit directed bridgehead metallation. Functionalisation of C2 is rare; Hou,[24] Pelter,[38] and Bolm[39] have all described the accidental/nonselective deprotonation of C2, but only Hopf has achieved deliberate 'lateral' functionalisation.[40]

Treatment of diastereoisomer (S_p,R_S)-**9** with lithium diisopropylamide (LDA) and MeI furnished a new compound **23** (16%) along with starting material (Scheme 6). Reaction of (R_p,S_S)-**9** with an alternative electrophile, diphe-



Scheme 6 Cyclisation of the C2 anion onto the tolyl moiety. *Reagents and conditions*: i. (a) LDA, THF, –78 °C, (b) MeI, (**23** 16%).



Scheme 7 Cyclisation of the C2 anion onto the tolyl moiety. *Reagents and conditions*: i. (a) LDA, THF, –78 °C, (b) Ph_2PCl (**24** 53%), **25** 10%); ii. (a) LDA, THF, –78 °C, (b) aq NH_4Cl (**26** 30%, **27** 14%).

nylphosphinic chloride, resulted in two new products, sulfoxide **24** (53%) and sulfide **25** (10%), as well as starting material (18%; Scheme 7). It was assumed that **24** and **25** were formed by the elimination of an adduct of a cyclohexadienyl anion and the phosphorous reagent. Empirical evidence supported this assumption as quenching the proposed anion with a weak acid resulted in the formation of 1,3-diene **26** (30%), conjugated diene **27** (14%) and unreacted starting material (12%). It appears that without a suitable leaving group, no re-aromatisation is possible. Presumably, 1,3-diene **26** predominates due to similar arguments to those proffered for the regiochemistry of the Birch reduction.

Initially, identification of the polycyclic compounds was taxing; all except **23** proved relatively unstable and thus were only characterised by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectra of **23** is complex and misleading, there is an unexpectedly large ^5J coupling between H17 and H20 (6.5 Hz) that presumably arises due to the doubly allylic nature of these hydrogen and their *pseudo* antiperiplanar arrangement. The structure was finally confirmed by X-ray crystallography (Figure 3). The presence of the sulfinyl moiety in **24** was inferred from the downfield shift of the *ortho* (H5) and *gem* (H13) hydrogen resonances; H5, 7.29–7.27 ppm and H13 7.17 ppm.[26] In [2.2]paracyclophane these equivalent protons are found at 6.46 ppm and in the methylated polycycle **23** they are at 7.12 and 6.98 ppm, respectively. The reduced sulfide **25** exhibits a high field resonance for the *ortho* H5 hydrogen

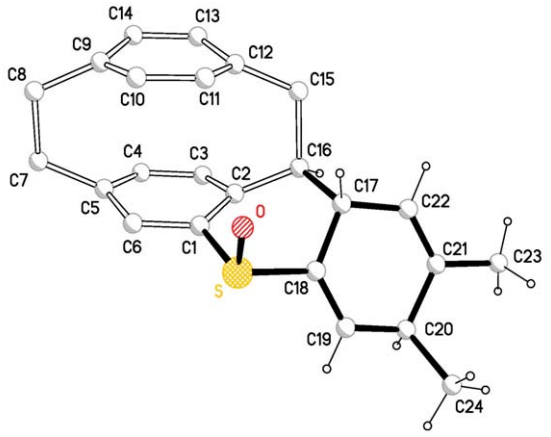


Figure 3 X-ray crystal structure of cyclisation product **23**[26b]

(6.52–6.49 ppm) suggesting that the electron-withdrawing sulfinyl moiety had been reduced to the electron-rich sulfide. The position of the alkene bonds in **26** and **27** was ascertained with the aid of NOE experiments; interaction between the methyl group and the CH_2 group of **26**, along with a large ^5J value for H17 and H20 analogous to **23** suggested the 1,3-diene pattern of **26**. The presence of the sulfinyl moiety as opposed to a simple sulfide was implied by the downfield resonance of H5, which at 7.14 ppm is almost identical to dimethyl **23** (7.12 ppm). The ^1H NMR spectrum of **27** indicated it was an isomer of **26** and NOE suggested the conjugated diene **27**. Again, the downfield resonance of H5 implied that the compound was in the sulfoxide oxidation state.

Clearly, the sulfinyl moiety can direct deprotonation to the bridgehead C2 position, but cyclisation on to the tolyl ring is faster than reaction with external nucleophiles.

4-Tolylsulfinyl[2.2]paracyclophane shows the potential of the proposed sulfoxide methodology to deliver a variety of enantiomerically pure [2.2]paracyclophane derivatives from a common precursor. Employing this sulfoxide, we have prepared enantiomerically pure 4-substituted [2.2]paracyclophane derivatives and functionalised the C13 position of the second aromatic ring, thus permitting the formation of disubstituted derivatives. Directed metallations are possible, but the C2 anion cyclises on to the toluene ring faster than it reacts with an external electrophile.

We are currently modifying the sulfoxide substituent in the hope of overcoming these limitations. The *tert*-butylsulfinyl group has proven successful in directed lithiation reactions, but is not without its own deficiencies,[30] and studies are now focussing on other sulfoxides. We are also interested in developing more efficient routes to various enantiomerically pure sulfoxides including oxidative kinetic resolution of racemic sulfides. The results of these studies will be reported in due course.

Et_2O and THF were obtained by distillation from sodium/benzophenone. CH_2Cl_2, toluene, and MeCN were distilled from CaH_2. Petroleum refers to the fraction of hexanes of boiling point 60–80 °C. All other chemicals were purchased from Avocado, Acros, or Sigma-Aldrich and were used without further purification.

Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were recorded using a Perkin-

Elmer PE241 polarimeter using a 1 dm path length cell and a concentration, *c*, in g/100 mL. IR spectra were recorded on a Perkin-Elmer 1710 Fourier transform spectrometer. NMR spectra were recorded on a Bruker DPX 300 Fourier transform instrument or by the late Dr. A. G. Avent using a Bruker AMX 500 Fourier transform instrument. Chemical shifts are given in ppm using residual undeuterated solvent peaks and TMS as internal references. Mass spectra were recorded at the University of Sussex by Dr. A. Abdul-Sada using a Kratos MS 80RF (FAB), VG Autospec (EI), Bruker BioApex III (ESI) double focussing spectrometers or a 4.7 FT-ICR (Bruker BioApex III) spectrometer.

X-ray crystallographic structure analysis experiments were conducted at the University of Sussex by Dr. P. B. Hitchcock using a Bruker-Nonius Kappa CDD diffractometer.

(R_p,S_s)-4-*p*-Toluenesulfinyl[2.2]paracyclophane [(R_p,S_s)-9] and (S_p,S_s)-4-*p*-Toluenesulfinyl[2.2]paracyclophane [(S_p,S_s)-9][22]

n-BuLi (2.5 M solution in hexane, 14.6 mL, 36.90 mmol) was added dropwise to a solution of (±)-4-bromo[2.2]paracyclophane (10.0 g, 34.80 mmol) in THF (174 mL) at –78 °C. The resulting yellow solution was stirred for 2 h at –78 °C, then added via cannula to a solution of (1*R*,2*S*,5*R*)-(–)-menthyl (*S*)-*p*-toluenesulfinate (10.8 g, 36.60 mmol) in THF (183 mL) at –78 °C. The solution was warmed to r.t. over 18 h. Sat. aq NH_4Cl (150 mL) was added and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 × 150 mL) and the combined organics dried ($MgSO_4$), then concentrated under reduced pressure to yield a yellow residue, which was purified by column chromatography on silica gel using gradient elution (petrol to 9:1 petrol–EtOAc) to give (R_p,S_s)-**9** as a white crystalline solid (3.7 g, 31%), and (S_p,S_s)-**9** as white needles (3.6 g, 30%).

(R_p,S_s)-9

Mp 175–177 °C (Lit. mp 176–177 °C); R_f = 0.4 (2:1 petrol–EtOAc); $[\alpha]_D^{25}$ –51.4 (*c* 1.1, $CHCl_3$) {Lit. $[\alpha]_D$ –51 (*c* 0.2, $CHCl_3$)}.

IR (nujol): 2923, 2725, 1903, 1585, 1459, 1377, 1303, 1155, 1079, 1035, 942, 910, 896, 727, 694 cm^{-1}.

^1H NMR (300 MHz): δ = 7.39 (2 H, d, *J* = 8.1 Hz, H-Tol), 7.25 (2 H, d, *J* = 7.7 Hz, H-Tol), 6.88 (1 H, d, *J* = 6.6 Hz, H13), 6.60–6.53 (4 H, m, H5, H7, H15, H16), 6.46 (1 H, d, *J* = 8.3 Hz, H8), 6.37 (1 H, d, *J* = 8.1 Hz, H12), 3.84 (1 H, ddd, *J* = 13.0, 10.6, 2.4 Hz, H2), 3.36 (1 H, ddd, *J* = 12.8, 10.6, 5.0 Hz, H1) 3.21–2.89 (5 H, m, H1, 2 × H9, 2 × H10), 2.79 (1 H, ddd, *J* = 12.9, 10.8, 5.2 Hz, H2), 2.38 (3 H, s, CH_3).

^{13}C NMR (75 MHz): δ = 142.0, 142.0, 141.8, 140.8, 140.7, 139.9, 139.1, 137.5, 136.5, 133.1, 132.7, 132.6, 132.5, 132.4, 129.6, 125.2, 35.5, 35.1, 34.9, 32.9, 21.4.

HRMS-ESI: *m*/*z* found 346.139135 $[M]^+$; $C_{23}H_{22}OS$ requires 346.139137.

(S_p,S_s)-9

Mp 148–150 °C (Lit. mp 151–155 °C); R_f = 0.3 (2:1 petrol–EtOAc); $[\alpha]_D^{25}$ +104.8 (*c* 1.2, $CHCl_3$) {Lit. $[\alpha]_D$ +85 (*c* 0.4, $CHCl_3$) containing ~8% other diastereoisomer}.

IR (nujol): 2921, 2725, 1903, 1584, 1459, 1377, 1303, 1180, 1077, 1055, 1035, 942, 897, 846, 815, 846, 815, 792, 727, 694 cm^{-1}.

^1H NMR (300 MHz): δ = 7.37 (2 H, d, *J* = 8.1 Hz, H-Tol), 7.17 (2 H, d, *J* = 8.0 Hz, H-Tol), 7.13 (1 H, d, *J* = 1.9 Hz, H5), 6.97 (1 H, d, *J* = 8.0 Hz, H13), 6.63 (1 H, d, *J* = 8.0 Hz, H12), 6.60 (1 H, dd, *J* = 7.9, 1.5 Hz, H7), 6.53 (2 H, s, H15, H16), 6.44 (1 H, d, *J* = 7.7 Hz, H8), 3.50 (1 H, ddd, *J* = 13.2, 10.3, 2.4 Hz, H2) 3.34 (1 H, ddd, *J* = 13.1, 9.9, 5.3 Hz, H1), 3.22–3.02 (5 H, m, H1, 2 × H9, 2 × H10), 2.87 (1 H, ddd, *J* = 13.5, 10.7, 5.3 Hz, H2), 2.30 (3 H, s, CH_3).

^{13}C NMR (75 MHz): δ = 144.3, 142.1, 141.9, 141.3, 139.6, 139.0, 136.5, 135.8, 135.3, 133.1, 132.9, 132.8, 131.5, 129.9, 127.8, 125.7, 35.2, 35.2, 34.6, 32.9, 21.3.

MS (EI+): *m*/*z* = 346 $[M]^+$, 329 $[M - O]^+$, 283, 257, 242, 225, 211, 178, 165, 150, 137, 121, 104, 91.

HRMS-EI: *m*/*z* found 346.138971 $[M]^+$; $C_{23}H_{22}OS$ requires 346.139137.

4-Substituted [2.2]Paracyclophane Derivatives; General Procedure

A solution of *t*-BuLi (1.5 M in pentane; 0.48 mmol, 4.0 equiv) was added dropwise to a solution of (S_p,R_S)-4-*p*-toluenesulfinyl [2.2]paracyclophane (0.12 mmol, 1 equiv) in THF (0.1 M) at –78 °C. The resulting orange solution was stirred at –78 °C for 10 min, whereupon the electrophile (0.96 mmol, 8 equiv) was added. Liquids were added neat and solids added as a solution in THF. The reaction mixture became a pale yellow colour and was stirred at –78 °C for a minimum of 3 h. Sat. aq NH_4Cl (5 mL) was added and the reaction mixture warmed to r.t. The organic layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography on silica gel using gradient elution (petrol to petrol–EtOAc).

(S_p)-4-Formyl[2.2]paracyclophane (1b)[13,41]

Prepared according to the general procedure and isolated as a white crystalline solid (0.02 g, 81%); data in general agreement with literature. See Supporting Information.[13,41]

(R_p)-4-Carboxy[2.2]paracyclophane (1c)[14,32]

Prepared according to the general procedure except for purification, which was performed by forming the carboxylate anion with aq 1 M NaOH, washing with CH_2Cl_2 (3 × 15 mL) before acidification with concd HCl and filtering the white percipitate (0.28 g, 77%); data in general agreement with literature. See Supporting Information.[14,32]

(S_p)-4-Hydroxy[2.2]paracyclophane (1d)[11,15]

Prepared according to the general procedure except after reacting with trimethyl borate for 30 min at –78 °C and r.t. for 1 h, *N*-methylmorpholine-*N*-oxide (10 equiv) was added and the reaction mixture heated to reflux for 2 days. Standard purification gave **1d** as a white solid (0.02 g, 53%); data in general agreement with literature. See Supporting Information.[11,15]

(S_p)-4-Amino[2.2]paracyclophane (1e)[42]

A solution of *t*-BuLi (1.8 M in hexane; 8.45 mL, 15.21 mmol, 4.0 equiv) was added dropwise to a solution of sulfoxide **10** (1.05 g, 3.04 mmol, 1.0 equiv) in THF (30.41 mL) at –78 °C. The bright yellow solution was stirred for 3 min and then a solution of TsN_3 (6.00 g, 30.41 mmol, 10.0 equiv) in THF (10.00 mL) was added in one portion. The reaction mixture was warmed to r.t. overnight. The reaction was poured into brine (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organics were dried ($MgSO_4$) and concentrated. The crude residue was dry loaded and filtered through silica using petrol (60–80) as eluent. The azide (0.84 g, 3.37 mmol, 1.0 equiv), $NaBH_4$ (2.50 g, 67.40 mmol, 20.0 equiv), and Bu_4NI (0.50 g, 1.35 mmol, 0.4 equiv) were suspended in 2:1 THF–H_2O (102 mL) and stirred at r.t. for 12 h. The reaction mixture was poured into brine (50 mL) and extracted with Et_2O (3 × 60 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (gradient neat petrol then 4:1 petrol–EtOAc) to give amine **1e** (0.20 g, 30%); data in general agreement with literature. See Supporting Information.[42]

(R_p)-4-Methyl[2.2]paracyclophane (1h)[32,43]
Prepared according to the general procedure and isolated as a white solid (0.03 g, 75%); data in general agreement with literature. See Supporting Information.[32,43]

(R_p)-4-Trimethylsilyl[2.2]paracyclophane (1i)
Prepared according to the general procedure and isolated as a white solid (0.38 g, 44%); mp 89–90 °C; R_f = 0.6 (2:1 petrol–EtOAc); $[\alpha]_D^{32}$ –59.01 (*c* 1.49, $CHCl_3$).

IR (CH_2Cl_2 film): 3435, 2952, 2854, 2893, 2107, 1638, 1464, 1435, 1243, 1180, 1066, 901, 832, 791, 753, 665 cm^{-1}.

^1H NMR (300 MHz): δ = 6.69 (1 H, d, *J* = 1.5 Hz, H5), 6.58 (2 H, br s, H15, H16), 6.43 (1 H, dd, *J* = 7.6, 1.5 Hz, H7), 6.39–6.28 (3 H, m, H12, H13, H8), 3.31–2.91 (8 H, m, 2 × H1, 2 × H2, 2 × H9, 2 × H10), 0.31 (9 H, s, 3 × CH_3).

^{13}C NMR (75 MHz): δ = 145.6, 139.5, 139.4, 138.9, 137.8, 137.1, 134.0, 133.6, 132.8, 132.5, 132.2, 132.1, 35.7, 35.5, 35.2, 35.2, 0.4.

MS: *m*/*z* not available as the compound did not ionise.

(R_p)-Diphenyl([2.2]paracyclophan-4-yl)phosphine Oxide (1j)[11]
Prepared according to the general procedure and isolated as a pale yellow solid (0.03 g, 49%); mp 192–194 °C (Lit.[11] mp 205–207 °C); R_f = 0.1 (2:1 petrol–EtOAc); $[\alpha]_D^{32}$ –68.3 (*c* 1.88, $CHCl_3$) {Lit.[11] $[\alpha]_D^{20}$ –24.1 (*c* 1.05, $CHCl_3$)}.

IR (neat): 3583, 3430, 2925, 2853, 1637, 1501, 1456, 1437, 1178, 1116, 1104, 1069, 1027, 998, 916, 851, 794, 752, 720, 707, 695, 665 cm^{-1}.

^1H NMR (300 MHz): δ = 7.72–7.68 (2 H, m, C_6H_5), 7.56–7.44 (6 H, m, C_6H_5), 7.38–7.35 (2 H, m, C_6H_5), 7.18 (1 H, dd, *J* = 7.88, 1.6 Hz, H5), 6.62 (1 H, d, *J* = 7.6 Hz, H7), 6.57 (1 H, dd, *J* = 7.9, 1.8 Hz, H15), 6.55 (1 H, d, *J* = 3.6 Hz, H8), 6.53 (1 H, dd, 7.8, 1.7 Hz, H16), 6.29 (1 H, dd, *J* = 2.1, 2.1 Hz, H12), 6.27 (1 H, dd, *J* = 3.5, 1.7 Hz, H13), 3.55–3.50 (2 H, m, H1, H2), 3.13–2.74 (6 H, m, H1, H2, 2 × H9, 2 × H10).

^{13}C NMR (75 MHz): δ = 146.1, 146.0, 140.0, 139.5, 139.4, 136.9, 136.7, 136.2, 134.8, 132.7, 132.3, 132.1, 132.0, 131.8, 131.5, 131.4, 131.3, 128.4, 128.3, 128.2, 128.1, 35.6, 35.1, 35.0, 29.7.

^{31}P NMR (300 MHz): δ = 28.12 (P).

MS (EI+): *m*/*z* = 408 [M^+], 304, 234, 225, 201, 178, 165, 152, 125, 104, 77.

HRMS-EI: *m*/*z* found 431.1535230; $C_{28}H_{25}PO$ + Na requires 431.1535230.

(R_p)-4-Deuterio[2.2]paracyclophane (1k)[44]
Prepared according to the general procedure and isolated as a white solid (0.15 g, 48%); mp 279–280 °C (Lit.[44] mp 280–285 °C); R_f = 0.7 (2:1 petrol–EtOAc); $[\alpha]_D^{32}$ +5.91 (*c* 0.16, $CHCl_3$) {Lit.[44] $[\alpha]_D^{25}$ –4 (*c* 0.87, $CHCl_3$) for the *S*-enantiomer}.

^1H NMR (300 MHz): δ = 7.14 (7 H, s, H5, H7, H8, H12, H13, H15, H16), 3.74 (8 H, s, 2 × H1, 2 × H2, 2 × H9, 2 × H10).

^{13}C NMR (75 MHz): δ = 139.6, 133.0, 35.7.

MS (EI+): *m*/*z* = 209 [$M]^+$, 104.

(S_p,S_s)-4-Bromo-13-*p*-tolylsulfinyl[2.2]paracyclophane [(S_p,S_s)-15] and (R_p)-4,12-Dibromo-7-*p*-tolylsulfanyl[2.2]paracyclophane
A solution of Br_2 (2.53 mL, 49.04 mmol, 10.5 equiv) in CH_2Cl_2 (490 mL) was covered with aluminum foil. Part of this solution (49 mL) was added iron filings (0.78 g, 14.01 mmol, 3 equiv) in a foil-coated flask and stirred at r.t. for 40 min. (R_p,S_s)-*p*-Tolylsulfinyl[2.2]paracyclophane (1.61 g, 4.67 mmol, 1 equiv) in THF (94 mL) was added in one portion. The remaining bromine solution was then added dropwise via cannula and the suspension stirred at r.t. for 20 h. The reaction mixture was poured into sat. aq NH_4Cl (100 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with aq 10% $Na_2S_2O_3$ (250 mL), brine (250 mL), dried ($MgSO_4$), and concentrated to yield a pale yellow residue. The residue was purified by recrystallisation (toluene–petrol) to give a white solid (38%) and (R_p)-4,12-dibromo-7-*p*-tolylsulfanyl[2.2]paracyclophane, which was purified by recrystallisation (CH_2Cl_2–Et_2O) to give a white solid (11%). In addition a molecule that appears to be (S_p)-4,12,18-tribromo-7-*p*-tolylsulfanyl[2.2]paracyclophane co-crystallised with the dibromide in about a 2:1 ratio.[33]

(S_p,S_s)-15
Mp 201–203 °C; R_f = 0.1 (2:1 petrol–Et_2O); $[\alpha]_D^{29}$ +92.5 (*c* 0.52, $CHCl_3$).

IR (nujol): 3435, 2109, 1644, 1473, 1394, 1081, 1031, 665 cm^{-1}.

^1H NMR (300 MHz): δ = 7.67 (2 H, d, *J* = 8.1 Hz, H-Tol), 7.31 (2 H, d, *J* = 7.9 Hz, H-Tol), 6.63–6.52 (4 H, m, H7, H8, H15, H16), 6.40 (1 H, s, H5), 5.85 (1 H, s, H12), 4.35 (1 H, ddd, *J* = 13.9, 9.7, 4.5 Hz, H1), 3.73 (1 H, ddd, *J* = 13.2, 10.1, 3.2 Hz, H2), 3.21 (1 H, ddd, *J* = 13.7, 10.1, 3.2 Hz, H9), 3.07–2.89 (5 H, m, H1, H2, H9, 2 × H10), 2.41 (3H, s, CH_3).

^{13}C NMR (75 MHz): δ = 147.3, 142.0, 141.6, 140.4, 140.0, 139.7, 139.8, 137.5, 136.3, 135.3, 132.0, 130.3, 128.4, 127.3, 127.2, 36.3, 35.2, 34.8, 32.3, 22.0.

MS (EI+): *m*/*z* = 426 [$M]^+$, 408, 345 [M – $^{81}Br]^+$, 318, 242, 225, 135, 91.

HRMS-EI: *m*/*z* found 425.0569250 [$M]^+$; $C_{23}H_{22}BrOS$ [$M]^+$ requires 425.0593280.

(R_p)-4,12-Dibromo-7-*p*-tolylsulfanyl[2.2]paracyclophane
Mp 161–162 °C; R_f = 0.7 (2:1 petrol–Et_2O); $[\alpha]_D^{31}$ +75.0 (*c* 0.88, $CHCl_3$).

IR (nujol): 3401, 3053, 2931, 2855, 2305, 1584, 1490, 1462, 1390, 1354, 1264, 1207, 1115, 1063, 1032, 907, 895, 876, 862, 844, 802, 750, 705, 665 cm^{-1}.

^1H NMR (300 MHz): δ = 7.20 (1 H, dd, *J* = 8.0, 1.2 Hz, H15), 6.97 (2 H, d, *J* = 7.9 Hz, H-Tol), 6.89 (2 H, d, *J* = 8.5 Hz, H-Tol), 6.71 (2 H, br s, H5, H13), 6.59 (1 H, s, H8), 6.51 (1 H, d, *J* = 7.9 Hz, H16), 3.79–3.67 (2 H, m, H2, H10), 3.40 (1 H, ddd, *J* = 12.9, 10.5, 2.1 Hz, H9), 3.16 (1 H, ddd, *J* = 13.0, 10.0, 6.1 Hz, H1), 3.06–2.94 (2 H, m, H1, H9), 2.89–2.68 (2 H, m, H2, H10), 2.24 (3 H, s, CH_3).

^{13}C NMR (75 MHz): δ = 143.7, 143.4, 142.8, 142.6, 139.8, 139.8, 139.2, 139.0, 136.6, 136.6, 134.4, 133.2, 130.0, 128.9, 128.5, 124.1, 35.5, 35.0, 33.3, 32.8, 21.4.

MS (EI+): *m*/*z* 488 [$M]^+$, 444, 410, 304, 225, 192, 149, 105, 84.

HRMS-EI: *m*/*z* found 508.9526950 [$M]^+$; $C_{23}H_2Br_2S$ + Na [M + Na]$^+$ requires 508.9544676.

(S_p)-4-Bromo-13-*p*-tolylsulfanyl[2.2]paracyclophane [(S_p)-19]
To a solution of (S_p,S_S)-**15** (0.30 g, 0.71 mmol, 1.0 equiv) in THF (9.4 mL) was added Et_3N (0.93 mL, 7.06 mmol, 10 equiv) followed by trichlorosilane (1.07 mL, 10.59 mmol, 15 equiv). The reaction was heated to reflux for 20 h. The reaction was carefully (***Caution!***) poured into a rapidly stirred mixture of aq 2 M NaOH (30 mL) and CH_2Cl_2 (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to yield a white solid, which was purified by recrystallisation (CH_2Cl_2–Et_2O), to furnish (S_p)-**19** as colourless crystals (0.28 g, 98%); mp 148–150 °C; R_f = 0.7 (2:1 petrol–EtOAc); $[\alpha]_D^{31}$ +10.2 (*c* 0.98, $CHCl_3$).

IR (neat): 3411, 2926, 2859, 2111, 1640, 1490, 1389, 1031, 804, 666 cm^{-1}.

^1H NMR (300 MHz): δ = 7.05 (2 H, d, *J* = 8.1 Hz, H-Tol), 6.97 (2 H, d, *J* = 8.3 Hz, H-Tol), 6.87 (1 H, s, H5), 6.78 (1 H, s, H12), 6.70–6.57 (4 H, m, H7, H8, H15, H16), 3.92–3.61 (2 H, m, H1, H2), 3.20–2.96 (6 H, m, H1, H2, 2 × H9, 2 × H10), 2.33 (3 H, s, CH_3).

^{13}C NMR (75 MHz): δ = 142.4, 141.1, 139.8, 138.7, 138.1, 136.0, 135.9, 135.2, 135.1, 134.8, 134.5, 133.7, 131.9, 129.5, 127.9, 126.3, 35.1, 34.7, 34.6, 32.9, 20.9.

MS (EI+): *m*/*z* = 408 $[M]^+$, 383, 328, 305, 290, 224, 210, 192.

HRMS-EI: *m*/*z* found 408.054001 $[M]^+$; $C_{23}H_{21}BrS$ $[M]^+$ requires 408.054734.

(S_p,S_s)-4-*p*-Tolylsulfinyl-13-methyl[2.2]paracyclophane [(S_p,S_s)-20]

To a solution of *i*-PrMgCl (0.07 mL, 0.14 mmol, 1.2 equiv) in THF (0.24 mL) at 0 °C was added *n*-BuLi (2.5 M in hexanes; 0.11 mL, 0.28 mmol, 2.3 equiv) and the resulting solution stirred at 0 °C for 10 min. A solution of (R_p,S_S)-**15** (0.05 g, 0.12 mmol, 1 equiv) in THF (1.2 mL) was added dropwise to the dibutylisopropylmagnesate solution. The resulting bright yellow solution was stirred for 30 min at 0 °C. MeI (0.01 mL, 0.16 mmol, 1.3 equiv) was added to give a pale yellow solution. After 1 h, more MeI (0.05 mL, 0.08 mmol, 0.7 equiv) was added to produce a colourless solution. The reaction mixture was poured into sat. aq NH_4Cl (10 mL) and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by column chromatography (gradient elution; petrol to petrol–EtOAc, 2:1) to yield (S_p,S_s)-**20** as a white solid (0.02 g, 48%); mp 162–163 °C; R_f = 0.2 (2:1 petrol–EtOAc); $[\alpha]_D^{31}$ +12.6 (*c* 1, $CHCl_3$).

IR (neat): 3052, 2927, 2852, 2305, 1579, 1490, 1470, 1449, 1265, 1087, 1051, 1017, 947, 896, 871, 838, 810, 748, 704, 665 cm^{-1}.

^1H NMR (500 MHz): δ = 7.26 (2 H, d, *J* = 8.3 Hz, H-Tol), 7.21 (1 H, d, *J* = 1.9 Hz, H5), 7.10 (2 H, d, *J* = 7.9 Hz, H-Tol), 6.60 (1 H, dd, *J* = 7.7, 1.9 Hz, H7), 6.50 (1 H, d, *J* = 7.7 Hz, H15), 6.77 (1 H, d, *J* = 1.9 Hz, H12), 6.44 (1 H, dd, *J* = 7.7, 0.7 Hz, H16), 6.29 (1 H, d, *J* = 1.5 Hz, H8), 3.70 (1 H, ddd, *J* = 13.7, 10.0, 5.3 Hz, H2), 3.55 (1 H, ddd, *J* = 13.3, 10.2, 2.7 Hz, H1), 3.16–3.02 (5 H, m, H2, 2 × H9, 2 × H10), 2.93 (1 H, ddd, *J* = 13.4, 10.7, 5.3 Hz, H1), 2.36 (3 H, s, CH_3), 2.26 (3 H, s, CH_3-Tol).

^{13}C NMR (75 MHz): δ = 144.1, 143.4, 141.0, 140.9, 139.5, 138.1, 137.3, 136.4, 136.1, 135.5, 134.7, 134.0, 129.9, 129.8, 125.1, 124.7, 35.1, 34.7, 33.4, 30.8, 21.3, 19.8.

MS (EI+): *m*/*z* = 360 $[M]^+$, 242, 224, 211, 178, 140, 119, 105, 92, 77.

(R_p)-4-*p*-Tolylsulfonyl-13-methyl[2.2]paracyclophane [(R_p)-21]

n-BuLi (2.5 M in hexanes; 0.05 mL, 0.12 mmol, 1.0 equiv) was added dropwise to (S_p)-**18** (0.05 g, 0.12 mmol, 1.0 equiv) in THF (2.5 mL) at –78 °C to form a bright red solution. The reaction mixture was stirred for 5 min at –78 °C, then MeI (0.04 mL, 0.61 mmol, 5.0 equiv) was added to give a colourless solution. The reaction mixture was poured into sat. aq NH_4Cl (5 mL), the organic phase separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography on silica gel (gradient elution petrol to petrol–EtOAc, 2:1) to yield (R_p)-**21** as a yellow solid (0.02 g, 40%); mp 230–231 °C; R_f = 0.4 (2:1 petrol–EtOAc); $[\alpha]_D^{22}$ –2.4 (*c* 0.6, $CHCl_3$).

IR (nujol): 3583, 2930, 2854, 1719, 1585, 1538, 1493, 1476, 1393, 1315, 1305, 1192, 1084, 1057, 1032, 1120, 960, 909, 877, 839, 816, 733, 708, 688, 664 cm^{-1}.

^1H NMR (500 MHz): δ = 7.53 (2 H, d, *J* = 8.4 Hz, H-Tol), 7.32 (1 H, d, *J* = 1.8 Hz, H5), 7.13 (2 H, d, *J* = 8.0 Hz, H-Tol), 6.73 (1 H, br s, H7), 6.56–6.43 (3 H, m, H8, H15, H16), 6.26 (1 H, br s, H12), 3.63–3.58 (2 H, m, H1, H2), 3.22–3.12 (2 H, m, H9, H10), 3.01–2.85 (4 H, m, H1, H2, H9, H10), 2.34 (3 H, s, CH_3-C13), 2.30 (3 H, s, CH_3-Tol).

MS (EI+): *m*/*z* = 376 $[M]^+$, 193, 179, 156, 139, 119, 104, 91, 77.

HRMS-EI: *m*/*z* found 399.1422657 $[M + Na]^+$; $C_{24}H_{24}O_2S$ $[M + Na]^+$ requires 399.1557580.

(R_p)-Diphenyl(4-*p*-tolylsulfanyl[2.2]paracyclophan-13-yl)phosphine Oxide [(R_p)-22a]

n-BuLi (2.5 M in hexanes; 0.12 mL, 0.29 mmol, 2.4 equiv) was added dropwise to a solution of *i*-PrMgCl (0.07 mL, 0.14 mmol, 1.2 equiv) in THF (0.2 mL) at 0 °C and the resulting solution stirred at 0 °C for 10 min. A solution of (S_p)-**19** (0.05 g, 0.12 mmol, 1.0 equiv) in THF (1.2 mL) was added dropwise to the dibutylisopropylmagnesate solution, and the resulting pale yellow solution stirred for 1 h at 0 °C. Diphenylphosphinic chloride (0.07 mL, 0.37 mmol, 3.0 equiv) was added in one portion and the reaction warmed to r.t. slowly over 72 h. The reaction mixture was poured into sat. aq NH_4Cl (10 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (2 × 40 mL), dried ($MgSO_4$), and concentrated to yield (R_p)-**22a** as a white crystalline solid (0.06 g, 88%); mp 222–223 °C; R_f = 0.14 (petrol); $[\alpha]_D^{24}$ –1.5 (*c* 0.4, $CHCl_3$).

IR (neat): 3500, 2933, 1638, 1478, 1416, 1390, 1327, 1216, 1123, 1094, 1032, 977, 891, 868, 749, 708, 665 cm^{-1}.

^1H NMR (300 MHz): δ = 7.73–7.57 (4 H, m, C_6H_5), 7.40–7.22 (6 H, br s, C_6H_5), 6.79 (2 H, d, *J* = 7.3 Hz, H-Tol), 6.70 (2 H, d, *J* = 7.3 Hz, H-Tol), 6.61 (1 H, s, H12), 6.52 (1 H, s, H5), 6.40 (4 H, br s, H7, H8, H15, H16), 3.96–3.35 (4 H, m, H1, H2, H9, H10), 2.96–2.67 (4 H, m, H1, H2, H9, H10), 2.07 (3 H, s, CH_3).

^{13}C NMR (75 MHz): δ = 142.9, 141.5, 140.3, 139.1, 138.5, 136.4, 136.3, 135.6, 135.7, 135.5, 135.3, 134.1, 132.5, 132.3, 132.1, 132.0, 129.9, 129.0, 128.9, 128.9, 128.4, 126.8, 35.5, 35.1, 35.0, 33.4, 21.3.

MS: *m*/*z* not available as the compound did not ionise.

(R_p)-4-*p*-Tolylsulfanyl[2.2]paracyclophane [(R_p)-17], (R_p)-4-*p*-Tolylsulfanyl-13-methyl[2.2]paracyclophane [(R_p)-22b] and (S_p)-4-Iodo-13-*p*-tolylsulfanyl[2.2]paracyclophane [(S_p)-22c]

t-BuLi (1.5 M in pentane; 0.16 mL, 0.24 mmol, 2.0 equiv) was added dropwise to a solution of (S_p)-4-bromo-13-*p*-tolylsulfanyl[2.2]paracyclophane (0.05 g, 0.12 mmol) in THF (2.4 mL) at –78 °C to give a bright yellow solution. The reaction mixture was stirred for 10 min at –78 °C before MeI (0.02 mL, 0.37 mmol, 3.0 equiv) was added in one portion. The reaction warmed to r.t. over 20 h. The reaction mixture was poured into sat. aq NH_4Cl (10 mL) and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield a white residue. The crude mixture was purified by column chromatography on silica gel (gradient elution petrol to petrol–EtOAc 2:1) to yield (R_p)-4-*p*-tolylsulfanyl[2.2]paracyclophane [(R_p)-**17**] as colourless crystals (0.02 g, 55%), (R_p)-4-*p*-tolylsulfanyl-13-methyl[2.2]paracyclophane [(R_p)-**22b**] as a white solid (0.01 g, 34%), and (S_p)-4-iodo-13-*p*-tolylsulfanyl[2.2]paracyclophane [(S_p)-**22c**] as a white solid (0.01 g, 11%).

(R_p)-17

Mp 167–168 °C; R_f = 0.1 (petrol); $[\alpha]_D^{27}$ +48.3 (*c* 0.53, $CHCl_3$).

IR (neat): 3429, 2925, 2854, 2115, 1638, 1491, 1456, 1215, 1087, 757, 666 cm^{-1}.

^{1}H NMR (300 MHz): δ = 7.15 (2 H, d, *J* = 8.3 Hz, H-Tol), 7.12 (1 H, d, *J* = 2.0 Hz, H5), 7.07 (2 H, d, *J* = 8.3 Hz, H-Tol), 6.58–6.45 (4 H, m, H7, H8, H13, H15), 6.40 (1 H, dd, *J* = 7.7, 2.0 Hz, H16), 6.30 (1 H, d, *J* = 1.7 Hz, H12), 3.40 (1 H, ddd, *J* = 12.4, 10.2, 1.9 Hz, H2), 3.27 (1 H, ddd, *J* = 15.5, 12.1, 5.7 Hz, H1), 3.13–2.83 (5 H, m, H1, 2 × H9, 2 × H10), 2.76 (1 H, ddd, *J* = 13.0, 10.6, 5.5 Hz, H2), 2.32 (3 H, s, CH_3).

^{13}C NMR (75 MHz): δ = 141.4, 141.1, 140.0, 139.6, 136.8, 136.7, 135.5, 133.7, 133.3, 132.8, 132.4, 132.3, 130.4, 130.2, 129.5, 128.6, 35.7, 35.3, 34.8, 34.2, 21.5.

MS (EI+): *m*/*z* = 330 $[M]^+$, 315 $[M - CH_3]^+$, 226, 211, 134, 105, 91.

HRMS-EI: *m*/*z* found 353.1334425 $[M + Na]^+$; $C_{23}H_{22}S$ + Na $[M + Na]^+$ requires 353.1337260.

(R_p)-22b

Mp 172–173 °C; R_f = 0.7 (2:1 petrol–EtOAc).

IR (neat): 3583, 3400, 3052, 2927, 2852, 2305, 1579, 1490, 1470, 1449, 1265, 1087, 1051, 1017, 947, 896, 871, 838, 810, 700, 704, 665 cm^{-1}.

^{1}H NMR (500 MHz): δ = 6.98 (2 H, d, *J* = 8.0 Hz, H-Tol), 6.91 (2 H, d, *J* = 8.2 Hz, H-Tol), 6.71 (1 H, d, *J* = 1.8 Hz, H12), 6.58 (1 H, d, *J* = 7.7 Hz, H15), 6.55 (1 H, d, *J* = 7.8 Hz, H16), 6.50 (1 H, d, *J* = 1.7 Hz, H8), 6.46 (1 H, d, *J* = 1.8 Hz, H7), 6.27 (1 H, d, *J* = 1.7 Hz, H5), 3.70 (1 H, ddd, *J* = 9.1, 9.1, 10.6 Hz, H2), 3.50 (1 H, ddd, *J* = 10.9, 8.1, 8.1 Hz, H1), 3.11–2.87 (6 H, m, H1, H2, 2 × H9, 2 × H10), 2.38 (3 H, s, CH_3-C13), 2.26 (3H, s, CH_3-Tol).

^{13}C NMR (75 MHz): δ = 142.4, 140.0, 139.0, 138.1, 138.0, 137.5, 135.4, 135.1, 134.0, 134.0, 133.9, 133.4, 132.4, 130.2, 129.5, 127.9, 34.9, 34.8, 32.9, 32.7, 20.9, 20.6.

MS (EI+): *m*/*z* = 344 $[M]^+$, 330, 256, 226, 211, 193, 178, 149, 141, 127, 119, 111, 95.

(S_p)-4-Iodo-13-*p*-tolylsulfanyl[2.2]paracyclophane [(S_p)-22c]

R_f = 0.4 (2:1 petrol–EtOAc).

^{1}H NMR (500 MHz): δ = 7.00 (1 H, d, *J* = 1.8 Hz, H5), 6.97 (2 H, d, *J* = 8.0 Hz, H-Tol), 6.91 (2 H, d, *J* = 8.3 Hz, H-Tol), 6.74 (1 H, d, *J* = 1.9 Hz, H12), 6.61 (1 H, d, *J* = 7.9 Hz, H15), 6.58 (1 H, d, *J* = 1.3 Hz, H7), 6.55 (1 H, d, *J* = 1.8 Hz, H16), 6.52 (1 H, dd, *J* = 7.7, 0.6 Hz, H8), 3.80 (1 H, ddd, *J* = 13.5, 9.9, 3.8 Hz, H2), 3.61 (1 H, ddd, *J* = 13.7, 9.9, 3.7 Hz, H1), 3.16–2.94 (6 H, m, H1, H2, 2 × H9, 2 × H10), 2.25 (3 H, s, CH_3)

MS (EI+): *m*/*z* = 456 $[M]^+$, 225, 211, 178, 113.

Limited data due to decomposition of the product.

<2>(1,4)-Benenzo-<1>(6,9)-2,3-dimethyl-9,9a-dihydro-3*H*-thioxanthenophane-10-oxide (23)

n-BuLi (2.5 M in hexanes, 0.21 mL, 0.52 mmol, 2.2 equiv) was added dropwise to (*i*-Pr)$_2$NH (0.68 mL, 0.52 mmol, 2.2 equiv) in THF (1.7 mL) at 0 °C. The mixture was stirred for 40 min at 0 °C and 20 minutes at –78 °C. (S_p,R_s)-4-*p*-Toluenesulfinyl[2.2]paracyclophane [(S_p,R_s)-**9**; 0.08 g, 0.23 mmol, 1.0 equiv] in THF (2.9 mL) was added via cannula to produce a deep red colouration. The reaction mixture was stirred at –78 °C for 70 min, then MeI (0.02 mL, 0.23 mmol, 1.0 equiv) was added dropwise causing the reaction mixture to clear. The reaction was stirred for 4 h, whilst the cold bath slowly warmed, before sat. aq NH_4Cl (5 mL) was added. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics layers were washed with brine (3 × 5 mL), dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (gradient elution petrol to petrol–EtOAc, 2:1) to yield **23** as light brown crystals (0.03 g, 16%); mp 194–195 °C; R_f = 0.1 (2:1 petrol–EtOAc).

IR (neat): 3490, 3155, 2926, 2856, 1784, 1700, 1621, 1463, 1413, 1387, 1244, 1212, 1155, 1033, 1081, 911, 895, 730 cm^{-1}.

^{1}H NMR (500 MHz): δ = 7.12 (1 H, d, *J* = 1.8 Hz, H5), 6.98 (1 H, dd, *J* = 8.0, 1.9 Hz, H13), 6.64 (1 H, dd, *J* = 7.7, 1.9 Hz, H16), 6.61 (1 H, dd, *J* = 7.8, 1.9 Hz, H15), 6.47 (1 H, dd, *J* = 7.8, 1.8 Hz, H7), 6.45 (1 H, dd, *J* = 3.0, 1.6 Hz, H19), 6.37 (1 H, dd, *J* = 8.0, 1.8 Hz, H12), 6.33 (1 H, dd, *J* = 7.8, 0.9 Hz, H8), 5.86 (1 H, ddd, *J* = 4.7, 3.0, 1.5 Hz, H22), 3.99 (1 H, dddd, *J* = 6.5, 4.9, 3.2, 1.6 Hz, H17), 3.47–3.41 (2 H, m, H1, H2), 3.33 (1 H, dd, *J* = 13.5, 9.4 Hz, H1), 3.03–3.39 (4 H, m, 2 × H9, 2 × H10), 2.81–2.77 (1 H, m, H20), 1.83 (3 H, s, CH_3-24), 1.24 (3 H, d, *J* = 7.3 Hz, CH_3-23).

^{13}C NMR (75 MHz): δ = 141.0 (C), 139.4 (C), 138.7 (C), 138.3 (C), 137.6 (CH), 137.7 (CH), 137.0 (C), 134.5 (CH), 134.2 (CH), 134.2 (C), 134.1 (CH), 132.6 (CH), 132.1 (CH), 130.8 (CH), 121.9 (CH), 50.8 (CH), 44.4 (CH_2), 35.5 (CH), 35.1 (CH_2), 35.0 (CH), 34.7 (CH_2), 21.2 (CH_3), 19.3 (CH_3).

MS (EI+): *m*/*z* = 359 $[M]^+$, 343 $[M - O]^+$, 329, 255, 238, 224, 207, 192, 178, 165, 150, 138, 124, 104, 91.

HRMS-EI: *m*/*z* found: 361.1643080 $[M + H]^+$; $C_{24}H_{25}SO$ $[M + H]^+$ requires 361.1620625.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are X-ray crystallographic data for all diastereoisomers of sulfoxide **9**, bromides (S_p,S_S)-**15** and (R_p,S_S)-**15** and polycyclic **23**, as well as figures highlighting salient ^{1}H NMR shifts for sulfoxide **9** and polycyclic compounds **23**–**27** and full experimental for all compounds.

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(26) (a) Supporting Information contains X-ray crytallographic data, full experimental, and figures showing select NMR data. (b) CCDC-276960–276961 and CCDC-772176–772181 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; or deposit@ccdc.cam.ac.uk.

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