The synthesis of enantiomerically pure 4-substituted [2.2]paracyclophane derivatives by sulfoxide–metal exchange

Peter B. Hitchcock, Gareth J. Rowlands* and Rakesh Parmar

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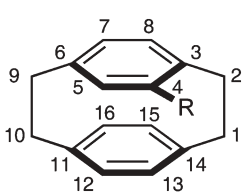
A general strategy for the synthesis of enantiomerically pure 4-substituted [2.2]paracyclophanes from a common sulfoxide precursor is described.

[2.2]Paracyclophane (22pc) **1a** and its derivatives are an intriguing family of compounds comprising of two eclipsed aromatic rings held in close proximity by two ethyl bridges (Fig. 1).[1] Considering the great potential of enantiopure 22pc derivatives in asymmetric synthesis,[2] it is surprising that research in this field is still in its infancy when compared to the analogous ferrocenyl[3] or η^6-arene transition metal complexes.[4] Undoubtedly, this is the result of a lack of attractive strategies for the preparation of enantiopure 22pc derivatives, with the area still dominated by tedious and frequently expensive resolution protocols. The optimum routes to the key enantiomerically pure monosubstituted 22pc derivatives appear to be: carboxylic acid **1b** *via* recrystallisation of diastereoisomeric (*p*-nitrophenyl)ethylammonium salts;[5] each enantiomer of the aldehyde **1c** *via* multiple recrystallisations of different Schiff bases;[6] phenol **1d** *via* esterification with (*S*)-(−)-camphanoyl chloride and multiple recrystallisations[7] or enzymatic resolution of the acetate;[8] amine **1e** *via* multiple recrystallisations of the diastereoisomeric salts formed from (*S*)-(+)-10-camphorsulfonic acid;[9] methyl ketone **1f** *via* HPLC[10] or diastereoisomeric SAMP-hydrazone derivatives.[11]

In order to overcome this severe limitation, we were interested in developing a general strategy that would facilitate the synthesis of any enantiomerically pure monosubstituted 22pc **1** derivative from a common precursor. We have a long-standing interest in the chemistry of sulfoxides[12] and were drawn to the possibility of utilising this moiety to both resolve the planar chirality and to direct the further functionalisation of the 22pc skeleton. The versatile reactivity of the sulfoxide group should allow directed metallations to either C2[13] or C5,[14] directed pseudo geminal bromination to C13 and direct sulfoxide–metal exchange at C4 (Fig. 1 shows substituted 22pc numbering).[15] In this communication we wish to report the first stage in our development of a versatile strategy for the synthesis of enantiomerically pure 22pc derivatives with the preparation of chiral monosubstituted [2.2]paracyclophanes.



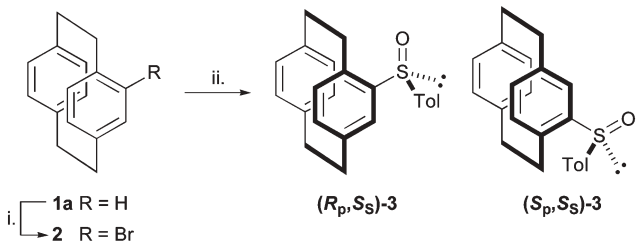
1a R = H **1f** R = $COCH_3$
1b R = CO_2H **1g** R = CH_3
1c R = CHO **1h** R = $SiMe_3$
1d R = OH **1i** R = $P(O)Ph_2$
1e R = NH_2

Fig. 1 [2.2]Paracyclophane and some derivatives.

Department of Chemistry, University of Sussex, Falmer, Brighton, UK BN1 9QJ. E-mail: g.rowlands@sussex.ac.uk; Fax: +44 1273 677 196; Tel: +44 1273 678 242

The known diastereoisomeric sulfoxides **3** can be readily prepared from 22pc in two steps:[16] bromination of 22pc furnished racemic (±)-4-bromo[2.2]paracyclophane **2**, which was subjected to halogen–metal exchange followed by reaction with commercially available Andersen's reagent, (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate or its enantiomer, to furnish the desired sulfoxides **3** in good yields (Scheme 1). The stereospecific sulfinylation proceeds with inversion of the sulfur stereocentre and the formation of two diastereoisomeric 22pc derivatives in a 1 : 1 ratio, which differ only by the planar chirality of the 22pc moiety. These are readily separated by simple column chromatography, thereby allowing the resolution of the planar chirality. The process appears to be scalable and we have performed the reaction on a 10 g scale at no detriment to the yield or the ease of separation of the diastereoisomers.† We have confirmed Reich and Yelm's[16] original assignment of relative stereochemistry, which was based on derivatisation, by X-ray crystallography (Fig. 2).‡

Having resolved the planar chirality of 22pc, *ipso*-substitution of the sulfur group *via* sulfoxide–metal exchange and the formation of 4-metallo[2.2]paracyclophane **4** was investigated (Scheme 2). Use of *n*-butyllithium, as described by Reich and Yelm,[16] gave predominantly 22pc **1a** with only a trace of the desired product **1c** (Table 1; Entry 1). Clearly, sulfoxide–metal exchange to give 4-lithio[2.2]paracyclophane **4** (M = Li) had occurred, but the anion was quenched at a faster rate than it underwent nucleophilic addition. Deeming that a "soft" 4-metallo[2.2]paracyclophane would be less basic, we utilised the sulfoxide–metal exchange conditions of Satoh *et al.* to form a cuprate.[17] Pleasingly, 4-methyl[2.2]paracyclophane **1g** was formed in good yield (61%) along with unreacted starting material (36%) (Entry 2). Use of [2.2]paracyclophan-4-ylmagnesium bromide **4** (M = MgBr) gave



Scheme 1 *Reagents and conditions*: (i) Br_2/Fe, DCM, rt, 98% (ii) (a) *n*-BuLi (1.05 eq.), THF, −78 °C (b) (S_S)-menthyl *p*-tolylsulfinate, THF, 61%.

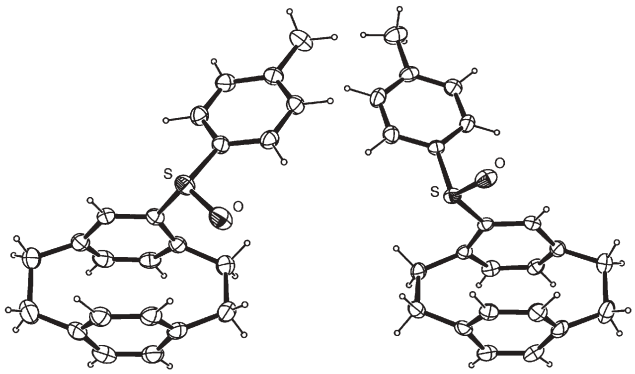
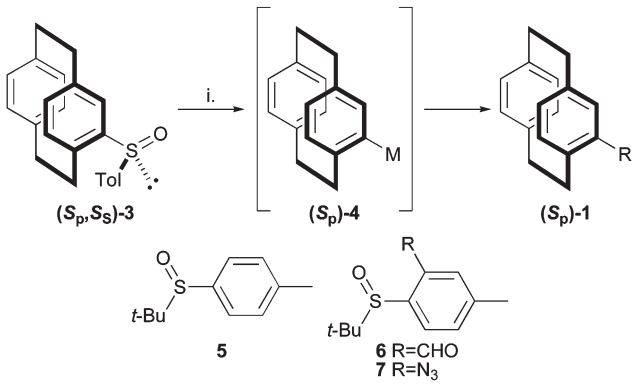


Fig. 2 X-Ray crystal structures of (R_p,S_S)-**3** (left) and (S_p,S_S)-**3** (right).



Scheme 2 *Reagents and conditions:* (i) All reactions were performed in THF (0.1 M) at −78 °C. See Table 1 for the organometallic reagents (R^1M) and electrophiles (RX).

comparable results (Entry 3). Unfortunately, when a less reactive electrophile (DMF) was used, only 22pc **1a** and unreacted starting material were recovered (Entry 4). Increasing the number of equivalents of Grignard reagent employed led to consumption of more starting material but still none of the desired product (Entry 5). The most likely source of protons was the ethylsulfoxide formed during sulfoxide–metal exchange, therefore, we turned our attention to *tert*-butyl organometallic reagents. Use of *tert*-butylmagnesium bromide proved unsatisfactory, with the recovery of starting material in poor yield (Entry 6), but *tert*-butyllithium proved more encouraging. All starting material was rapidly consumed and, on addition of methyl iodide, furnished the desired product **1g** (30%), 22pc **1a** (40%) and *tert*-butylsulfinyl-*p*-toluene **5** (16%) (Entry 7). More rewardingly, a good yield of 4-formyl[2.2]-paracyclophane **1c** (62%) could also be achieved (Entry 8). Interestingly, a third by-product, the aldehyde **6** (29%; Scheme 2), was isolated along with 22pc (27%) and **5** (15%), suggesting that the tolyl group was acting as the proton source for the formation of 22pc. Performing the reaction at 0 °C only appeared to accelerate the detrimental protonation step (Entries 9 and 10). Extensive optimisation produced conditions that minimised this adverse reaction and resulted in the formation of **1c** in good yield (Entry 11). The reaction is independent of the relative stereochemistry of the sulfoxide and 22pc moieties with all diastereoisomers giving comparable yields.

Next the generality of the reaction was investigated. Sulfoxide–metal exchange, under the optimised conditions,§ followed by addition of a variety of electrophiles furnished the desired 4-substituted [2.2]paracyclophanes **1** in moderate to excellent yields (Scheme 2 and Table 1; Entries 12–18).¶ Pleasingly, these results demonstrate that the methodology provides a simple, enantiospecific synthesis of four of the five key monosubstituted 22pc derivatives, the acid **1b**, the aldehyde **1c**, the alcohol **1d** and the amine **1e** from one common precursor. Whilst the yield of **1e** is not ideal (32% for two steps; substitution then reduction), 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 allows the preparation of the intriguing phosphine oxide **1i** in enantiomerically pure form for the first time *via* reaction with either diphenylphosphinyl chloride or chlorodiphenylphosphine (Entries 16 & 17); presumably, aerial oxidation occurs on purification in the latter example.

Table 1 Synthesis of 4-substituted [2.2]paracyclophane derivatives

Entry	R^1M (eq.)	RX (eq.)	Product	Yield (%)	**3** (%)	**1a** (%)	Other[a] (%)
1	*n*-BuLi (6.0)	DMF (12.0)	**1c**	<5	0	>95	—
2	EtMgBr (3.5), CuBr (0.5)	MeI (4.0)	**1g**	61	36	—	—
3	EtMgBr (3.5)	MeI (4.0)	**1g**	62	32	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)	**1g**	30	0	40	16 (**5**)
8	*t*-BuLi (2.0)	DMF (4.0)	**1c**	62	0	27	15 (**5**), 29 (**6**)
9[b]	*t*-BuLi (2.0)	DMF (4.0)	—	0	0	80	—
10[b]	*t*-BuLi (3.0)	DMF (6.0)	**1c**	16	0	45	15 (**5**), 21 (**6**)
11	*t*-BuLi (4.0)	DMF (8.0)	**1c**	81	0	18	—
12	*t*-BuLi (4.0)	MeI (8.0)	**1g**	64	0	20	—
13	*t*-BuLi (4.0)	TMSCl (8.0)	**1h**	44	25	21	—
14	*t*-BuLi (4.0)	CO_2 (xs)	**1b**	77	—	—	—
15	*t*-BuLi (4.0)	$B(OMe)_3$ (8.0)	**1d**	53[c]	0	43	—
16	*t*-BuLi (4.0)	$Ph_2P(O)Cl$ (8.0)	**1i**	52	11	35	—
17	*t*-BuLi (4.0)	Ph_2PCl (8.0)	**1i**[d]	90	0	5	—
18	*t*-BuLi (4.0)	TsN_3 (10)	**1e**	32[e]	0	54	13 (**5**), 20 (**7**)

[a] See Scheme 2. [b] Reaction performed at 0 °C. [c] Boron adduct was not isolated but oxidised *in situ* by the addition of NMO and 40 h reflux. [d] Phosphine is believed to oxidise on purification. [e] The azide was not isolated but reduced with $NaBH_4$, *n*-Bu_4NI in THF–H_2O to give the amine.

With other electrophiles, such as iodine, bromine and acetyl chloride, protonation of 4-lithio[2.2]paracyclophane **4** (M = Li) and recovery of 22pc was observed. Considering that all these electrophiles react with 4-lithio[2.2]paracyclophane generated from 4-bromo[2.2]paracyclophane, it is fair to assume that competitive *ortho*-lithiation of the tolylsulfoxide moiety hinders the reaction.

In conclusion, we have developed a versatile method for the preparation of a range of enantiomerically pure 4-substituted [2.2]paracyclophanes based on the use of the sulfoxide moiety to both resolve planar chirality and act as a precursor to the formation of 4-metallo[2.2]paracyclophane. The current work highlights one of the limitations of the tolylsulfoxide group for the elaboration of the 22pc skeleton. We are currently exploring the use of alternative sulfoxide moieties in this reaction and in directed metallations and brominations of the 22pc framework and these results will be published in due course.

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Notes and references

† (R_p,S_S)-4-*p*-Toluenesulfinyl[2.2]paracyclophane, (R_p,S_S)-**3**, and (S_p,S_S)-4-*p*-toluenesulfinyl[2.2]paracyclophane, (S_p,S_S)-**3**. To a solution of (±)-4-bromo[2.2]paracyclophane (10.0 g, 34.8 mmol, 1.0 eq.) in THF (174 mL) at −78 °C was added *n*-butyllithium (2.5 M in hexane; 14.6 mL, 36.9 mmol, 1.05 eq.). The resulting yellow solution was stirred for a further 2 h before being added in one portion to a solution of (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (10.8 g, 36.6 mmol, 1.05 eq.) in THF at −78 °C. The orange solution was warmed to room temperature overnight. The yellow reaction mixture was poured into saturated aqueous ammonium chloride solution and extracted with Et_2O (3 × 150 mL). The combined organics were dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography (neat petrol (60–80) to 9 : 1 petrol (60–80) : EtOAc) to give (R_p,S_S)-**3** as a crystalline solid (3.7 g, 31%); (R_f 0.4 2 : 1 petrol (60–80) : EtOAc); selected data: δ_H (300 MHz, $CDCl_3$) 7.40 (2H, d, *J* = 8.2 Hz, Tol-*H*), 7.25 (2H, d, *J* = 7.9 Hz, Tol-*H*), 6.79 (1H, d, *J* = 8.0 Hz, 13-H), 6.59–6.44 (4H, m, Ar-*H*), 6.45 (1H, d, *J* = 8.1 Hz, Ar-*H*), 6.38 (1H, d, *J* = 7.6 Hz, Ar-*H*), 3.83 (1H, ddd, *J* = 13.0 Hz, 10.5 Hz, 2.5 Hz, 2-H), 3.35 (1H, ddd, *J* = 12.9 Hz, 10.5 Hz, 4.9 Hz, 1-H), 3.16–2.93 (5H, m, CH_2), 2.79 (1H, ddd, *J* = 13.0 Hz, 10.5 Hz, 5.0 Hz, 2-H), 2.37 (3H, s, CH_3); δ_c (75 MHz, $CDCl_3$) 142.4, 141.6, 141.4, 141.2, 141.1, 140.4, 139.5, 138.0, 137.0, 133.5, 133.1, 132.98, 132.95, 132.8, 130.0, 125.6, 35.9, 35.6, 35.3, 33.3, 21.8; and (S_p,S_S)-**3** as a crystalline solid (3.6 g, 30%); (R_f 0.3 2 : 1 petrol (60–80) : EtOAc); selected data; δ_H (300 MHz, $CDCl_3$) 7.37 (2H, d, *J* = 8.2 Hz, Tol-*H*), 7.17 (2H, d, *J* = 8.0 Hz, Tol-*H*), 7.12 (1H, d, *J* = 1.7 Hz, H-5), 6.96 (1H, d, *J* = 8.0 Hz, 13-H), 6.60 (2H, d, *J* = 9.2 Hz, Ar-*H*), 6.53 (2H, s, Ar-*H*), 6.44 (1H, d, *J* = 7.7 Hz, Ar-*H*), 3.48 (1H, ddd, *J* = 13.2 Hz, 10.3 Hz, 2.4 Hz, 2-H), 3.33 (1H, ddd, *J* = 13.1 Hz, 9.9 Hz, 5.3 Hz, 1-H), 3.21–3.06 (5H, m, CH_2), 2.84 (1H, ddd, *J* = 13.5 Hz, 10.4 Hz, 5.3 Hz, 2-H), 2.30 (3H, s, CH_3); δ_c (75 MHz, $CDCl_3$) 144.7, 142.5, 142.3, 141.7, 140.0, 139.4, 136.9, 136.2, 135.8, 133.5, 133.3, 131.9, 130.3, 128.2, 126.1, 35.7, 35.6, 35.0, 33.3, 21.7. All other data in agreement with literature values.[16]

‡ Crystal data for (R_p,S_S)-**3**: $C_{23}H_{22}OS$, *M* = 346.47, *T* = 173(2) K, monoclinic, space group $P2_1$ (no. 4), *a* = 10.4226(2), *b* = 11.4979(2), *c* = 14.9892(2) Å, *β* = 95.392(1)°, *V* = 1788.33(5) Å^3, *Z* = 4, D_c = 1.29 Mg m^{-3}, *μ* = 0.19 mm^{-1}, independent reflections = 6305 [R_{int} = 0.051], *R*1 [for 5866 reflections with $I > 2\sigma(I)$] = 0.037, w*R*2 (all data) = 0.097. The H atoms were refined, with the exception of that on C16b which had to be put in riding mode. The reason is that there appears to be a very slight contamination by a product with a substituent at C16b. This is evidenced by a residual peak of *ca.* 1 electron at a distance of 1.54 Å from C16b. CCDC 276960. Crystal data for (S_p,S_S)-**3**: $C_{23}H_{22}OS$, *M* = 346.47, *T* = 173(2) K, orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 8.1055(2), *b* = 14.4647(4), *c* = 15.2330(5) Å, *V* = 1785.97(9) Å^3, *Z* = 4, D_c = 1.29 Mg m^{-3}, *μ* = 0.19 mm^{-1}, independent reflections = 3137 [R_{int} = 0.043], *R*1 [for 3032 reflections with $I > 2\sigma(I)$] = 0.026, w*R*2 (all data) = 0.069. CCDC 276961. See http://dx.doi.org/10.1039/b507394d for crystallographic data in CIF or other electronic format.

§ *Representative procedure*: A solution of *tert*-butyllithium (1.8 M in hexane; 8.45 mL, 15.21 mmol, 4.0 eq.) was added dropwise to a solution of sulfoxide **3** (1.05 g, 3.04 mmol, 1.0 eq.) in THF (30.41 mL) at −78 °C. The bright yellow solution was stirred for 3 min and then a solution of tosyl azide (6.00 g, 30.41 mmol, 10.0 eq.) in THF (10.00 mL) was added in one portion. The reaction mixture was warmed to room temperature overnight. The reaction was poured into brine (50 mL) and extracted with Et_2O (3 × 100 mL). 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 eq.), $NaBH_4$ (2.50 g, 67.40 mmol, 20.0 eq.) and *n*-Bu_4NI (0.50 g, 1.35 mmol, 0.4 eq.) were suspended in 2 : 1 THF : H_2O (102 mL) and stirred at room temperature for 12 h. The reaction was poured into brine (50 mL) and extracted with Et_2O (3 × 60 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (neat petrol then 4 : 1 petrol : EtOAc) to give amine **1e** (0.20 g, 30%). All data in agreement with literature values.[9]

¶ The enantiomeric purity was determined by comparison of optical rotations with literature values, with all values within 5%, and by the derivatisation of acid **1b** with a chiral amine and alcohol **1d** with Mosher's acid to give single diastereoisomers in both cases.

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