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The synthesis and directed *ortho*-lithiation of 4-*tert*-butylsulfinyl[2.2]paracyclophane†

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Received 14th July 2005, Accepted 7th September 2005
First published as an Advance Article on the web 26th September 2005

The *ortho*-lithiation of one diastereoisomer of 4-*tert*-butylsulfinyl[2.2]paracyclophane is the key step to the synthesis of a range of 4,5-disubstituted [2.2]paracyclophane derivatives.

[2.2]Paracyclophane (22pc) **1** is the parent molecule for a fascinating family of compounds comprising of two eclipsed aromatic rings held in close proximity by two ethyl bridges (Fig. 1).[1] The strong electronic interaction between the two rings combined with rigidly defined geometric relationships between substituents on 22pc give rise to the unique properties of these molecules and many derivatives show great promise in a diverse array of chemical disciplines.[2] Considering the great potential of enantiomerically pure 22pc derivatives, it is surprising that research in this field is still in its relative infancy[3,4] when compared to the analogous ferrocenyl[5] or η^6 arene transition metal complexes.[6] The most significant impediment to research in this field appears to be the lack of attractive strategies for the preparation of enantiomerically pure 22pc derivatives, with the area dominated by tedious and frequently expensive resolution protocols.[3]

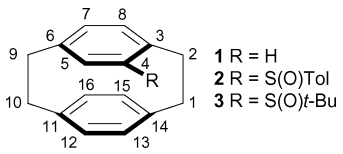
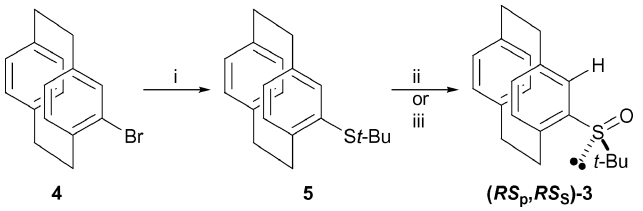


Fig. 1 [2.2]Paracyclophane and sulfoxide derivatives.

In order to overcome this severe limitation, we are interested in developing a general strategy for the synthesis of a range of enantiomerically pure 22pc derivatives based on the versatile chemistry of the sulfoxide moiety[7] and recently, we reported an efficient synthesis of enantiomerically pure 4-monosubstituted [2.2]paracyclophanes *via* direct sulfoxide–metal exchange of 4-tolylsulfinyl[2.2]paracyclophane **2**.[8] In this communication, we wish to report the synthesis of 4,5-disubstituted [2.2]paracyclophanes by directed *ortho*-lithiation of 4-*tert*-butylsulfinyl[2.2]paracyclophane **3** (Fig. 1).

Our initial investigations of directed metallations utilised the tolyl sulfoxide **2** (Fig. 1).[8] Whilst these gave a number of intriguing results, particularly those aimed at lateral H2 deprotonation, it rapidly became apparent that the tolyl group was not an inert substituent.[9] Therefore, we turned our attention to 4-*tert*-butylsulfinyl[2.2]paracyclophane **3**. In order to rapidly assess the efficacy of the *tert*-butylsulfinyl moiety at directing metallations on the 22pc framework,[10,11] we decided to prepare the racemic compound prior to expending resources preparing the enantiomerically pure variant (Scheme 1). (±)-4-Bromo[2.2]paracyclophane **4** smoothly underwent halogen–metal exchange and subsequent reaction with *tert*-butyl disulfide to furnish (±)-4-*tert*-butylsulfanyl[2.2]paracyclophane **5** in good yield (66%). Interestingly, oxidation of sulfide **5** with *m*-chloroperbenzoic acid resulted in the exclusive formation of just one diastereoisomer of sulfoxide **3** in excellent yield (94%).‡ Similarly, use of sodium periodate gave the same, single diastereoisomer in 80% yield. The relative stereochemistry was determined to be ($\boldsymbol{RS}_p$,$\boldsymbol{RS}_S$)-**3** by X-ray crystallography (Fig. 2)§ and indicated that the oxygen atom of the sulfoxide was orientated towards the *ortho* proton, H5. Presumably, the complete diastereoselectivity in the oxidation is the result of the sulfide existing in one conformation, with the *tert*-butyl group perpendicular to the decks of 22pc and the ethyl bridge blocking the approach of the oxidant to one face of the sulfide.



Scheme 1 *Reagents and conditions*: (i) a) *t*-BuLi, THF, −78 °C, b) $(t\text{-BuS})_2$, −78 °C–rt, 66%; (ii) *m*-CPBA, CH_2Cl_2, 0 °C, 94%; (iii) $NaIO_4$, dioxane–H_2O, rt, 80%.

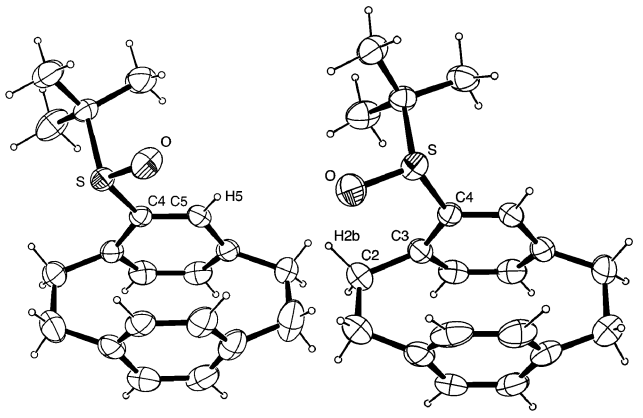
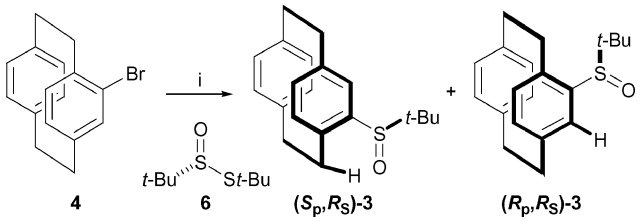


Fig. 2 X-Ray structures of ($\boldsymbol{RS}_p$,$\boldsymbol{RS}_S$)-**3** (left) and ($\boldsymbol{S}_p$,$\boldsymbol{R}_S$)-**3** (right).

Before studying the direct *ortho*-metallations it was deemed prudent to prepare the second diastereoisomer. A wide range of oxidising reagents were screened, but to no avail; either diastereoisomer ($\boldsymbol{RS}_p$,$\boldsymbol{RS}_S$)-**3** was formed, starting material was recovered or decomposition was observed. Having previously shown that reaction of (±)-4-lithio[2.2]paracyclophane with an enantiomerically pure sulfinylating reagent resulted in the clean formation of the two possible diastereoisomers,[8] we decided to convert **4** directly to the sulfoxides ($\boldsymbol{S}_p$,$\boldsymbol{R}_S$)-**3** and ($\boldsymbol{R}_p$,$\boldsymbol{R}_S$)-**3** by treatment with *n*-butyllithium followed by the addition of (*R*)-*tert*-butyl *tert*-butanethiosulfinate **6** (Scheme 2).[12] Pleasingly, two diastereoisomers were formed in a ratio of 1:1.4

† This paper is dedicated with respect and admiration to Professor Steven V. Ley on the occasion of his 60th birthday.

DOI:10.1039/b509994c



Scheme 2 *Reagents and conditions*: (i) a) *n*-BuLi, THF, −78 °C, b) **6**, THF, −78 °C, 72%.

(***S***$_p$,***R***$_S$)-**3**:(***R***$_p$,***R***$_S$)-**3** and a combined yield of 72%. The two diastereoisomers are readily separable from each other by column chromatography with the diastereoisomer (***R***$_p$,***R***$_S$)-**3**, corresponding to the product of oxidation, being eluted second. As the sulfinylation reaction is known to proceed with inversion at sulfur, the two diastereoisomers can only differ by the chirality of the 22pc portion. Therefore, this methodology allows the facile resolution of the planar chirality of 22pc. Once again, the relative stereochemistry was confirmed by X-ray crystallography and shows that the sulfoxide oxygen is orientated towards the bridge protons of C2 (Fig. 2).

Comparison of the two diastereoisomers suggests that one, (***R***$_p$,***R***$_S$)-**3**, will direct metallations to the *ortho*, C5, position, whilst the second, (***S***$_p$,***R***$_S$)-**3**, will direct a lateral metallation at C2.[13] The theory of the complex-induced proximity effect[14] states that the proton to be removed must be in the vicinity of the base which, in turn, should be complexed to the directing group. For directed *ortho*-metallation, the optimum geometry is believed to have the directing group planar to the arene ring with the oxygen atom close to the proton. The X-ray crystal structure of (***RS***$_p$,***RS***$_S$)-**3** shows that the sulfinyl group is close to this idealised geometry with a torsional angle between S–O and C4–C5 of 11.6°. We believe that the interaction between the *tert*-butylsulfinyl group and both the ethyl bridge and the lower deck of 22pc severely restricts rotation around the C4–S bond. Therefore, the conformation shown in the X-ray structure is maintained to a high degree in the solution phase as intimated by the ^{1}H NMR spectra. The sulfinyl group is known to exhibit a strong anisotropic effect resulting in a significant change in the chemical shift of protons in close proximity to the oxygen atom.[15] The *ortho* proton, H5, of diastereoisomer (***R***$_p$,***R***$_S$)-**3** displays a downfield shift when compared to (***S***$_p$,***R***$_S$)-**3** (7.01 *vs*. peak under 6.64–6.51 ppm) indicating the proximity of the sulfoxide oxygen (Fig. 3). Even more pronounced is the difference in chemical shifts for H2 in the two diastereoisomers, (***R***$_p$,***R***$_S$)-**3** shows a signal at 3.53 ppm whilst in (***S***$_p$,***R***$_S$)-**3** H2 is considerably more deshielded at 4.37 ppm, suggesting that the oxygen is in close vicinity to H2.

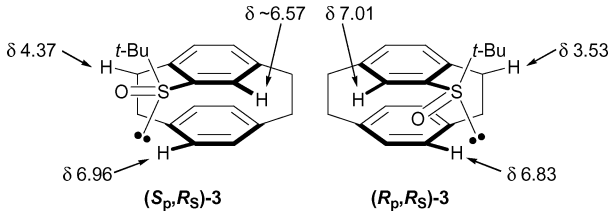


Fig. 3 Salient ^{1}H NMR shifts in ppm for each diastereoisomer.

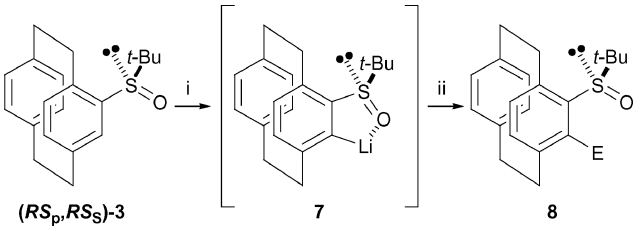
Utilising the racemic C5 orientated sulfoxide, (***RS***$_p$,***RS***$_S$)-**3**, we attempted the standard *ortho*-lithiation conditions for *tert*-butylsulfoxides reported by Snieckus (*n*-BuLi, THF, −78 °C, 1 h then addition of electrophile)[11] and were disappointed to only recover unreacted starting material. Intensive optimisation studies led to a number of observations. The *ortho*-lithiation is best achieved by the very slow addition of the base, normally, dropwise over a period of 30 minutes followed by further stirring for 1 hour; longer or shorter times result in a rapid decrease in yield. A minimum of two equivalents of base are required for efficient reaction and the solvent makes a crucial difference; if *n*-BuLi is used as the base, THF gives the optimum yield, whilst Et_2O should be used in conjunction with *t*-BuLi. TMEDA does not have a beneficial effect on either set of conditions. Finally, temperature plays a crucial role as the anion does not appear to react with any electrophile, except methyl iodide, below −40 °C. Presumably this is a steric effect, although further experimentation is still required to confirm this hypothesis. The optimum temperature for deprotonation is 0 °C with slow warming to room temperature after addition of the electrophile.

Table 1 Synthesis of disubstituted [2.2]paracyclophane derivatives **8**

Entry	Electrophile	E (compound)[a,b]	Yield (%)[c]
1	MeI	Me (**8a**)	75
2	Me_3SiCl	Me_3Si (**8b**)	62 (95[d])
3	I_2	I (**8c**)	53 (90[d])
4	CO_2	CO_2H (**8d**)	86
5	$ClCO_2i$-Bu	CO_2i-Bu (**8e**)	58 (98[d])
6	TsNCO	C(O)NHTs (**8f**)	35
7	$(PhS)_2$	SPh (**8g**)	59
8	TsN_3	NH_2 (**8h**)[e]	64
9	PhCHO	CH(OH)Ph (**8i**)	55 (63[d])
10	*i*-PrCHO	CH(OH)*i*-Pr (**8j**)	27 (49[d])

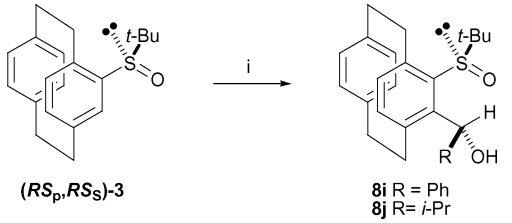
[a] Racemic sulfoxide was used in all reactions. [b] All compounds have been fully characterised. [c] Isolated yield of pure product. [d] Yield based on recovered starting material. [e] Azide was reduced *in situ* with $NaBH_4$.

Following optimisation of the directed *ortho*-lithiation, we were able to prepare a variety of 4,5-disubstituted [2.2]paracyclophanes **8** (Scheme 3; Table 1).¶ A wide range of electrophiles can be used effectively in the reaction (Entries 1–8). A number of the reactions stall at ~50% of the desired product, with the remainder of the material being unreacted starting material. It is interesting to speculate if this is the result of the formation of an organolithium hetero-aggregate.[16] Pleasingly, it is possible to introduce an amine at C5 (**8h**) *via* reaction with tosyl azide and *in situ* reduction. Enantiomerically pure derivatives of 5-amino-4-*tert*-butylsulfinyl[2.2]paracyclophane, **8h**, would be analogous to 2-amino-substituted 1-sulfinylferrocenes that have recently found use as ligands and catalysts in asymmetric synthesis.[17]



Scheme 3 The *ortho*-lithiation of 4-*tert*-butylsulfinyl[2.2]paracyclophane. *Reagents and conditions*: (i) *n*-BuLi (2 eq.), THF, 0 °C; (ii) electrophile (>4 eq.), 0 °C–rt.

Both aromatic aldehydes (benzaldehyde, Entry 9) and aliphatic aldehydes (isobutyraldehyde, Entry 10) undergo addition to give the alcohols **8i** and **8j** in moderate to poor yields (Scheme 4). The lower yield of **8j** may arise due to the preferential enolisation of isobutyraldehyde; we have reason to believe that



Scheme 4 *Reagents and conditions*: (i) a) *n*-BuLi (2 eq.), THF, 0 °C, b) RCHO (4 eq.), 0 °C–rt, R = Ph 55%; R = *i*-Pr 27%.

the anion, **7**, is very basic. Unfortunately, larger electrophiles, such as ketones, do not react. The reaction with both aldehydes occurs with complete diastereoselectivity, furnishing just one diastereoisomer. The configurations of the new stereocentres were determined from the X-ray crystal structures‖ of both adducts and were shown to be (***RS***$_p$,***RS***$_S$,***RS***)-**8i** and (***RS***$_p$,***RS***$_S$,***RS***)-**8j**. The selectivity can be rationalised if 4-*tert*-butylsulfinyl-5-lithio[2.2]paracyclophane **7** is divided into four sections (Fig. 4) and then three of the quadrants are considered to be blocked, one by the *tert*-butyl group and two by the lower deck of 22pc. Therefore, the aldehyde substituent approaches *via* the fourth quadrant and attack occurs on the *re* face of the carbonyl group. Interestingly, similar secondary alcohols can be formed by the highly diastereoselective addition of organometallic reagents to formyl[2.2]paracyclophane derivatives, indicating the highly effective nature of 22pc as a chiral auxiliary.[18]

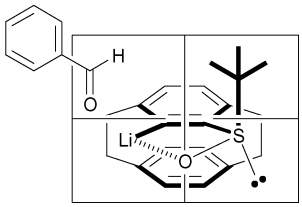


Fig. 4 Possible explanation for the complete diastereoselectivity in the addition of aldehydes.

In conclusion, we have developed an efficient method for the preparation of a range of 4,5-disubstituted [2.2]paracyclophanes *via* directed *ortho*-metallation of a *tert*-butylsulfinyl group. The fact that this moiety can be introduced in a stereospecific manner indicates that the current methodology could be utilised to both resolve the planar chirality of [2.2]paracyclophane and then functionalise [2.2]paracyclophane to furnish enantiomerically pure derivatives. We are currently investigating the use of a number of these derivatives, in particular, 5-amino-4-*tert*-butylsulfinyl[2.2]paracyclophane **8h**, in a range of catalytic asymmetric processes. Furthermore, we are continuing to study the chemistry of a range of 4-sulfinyl[2.2]paracyclophanes as a means of elaborating the [2.2]paracyclophane backbone at alternative positions[19] and these results will be published in the near future.

Notes and references

‡ Synthesis of (*RS*$_p$,*RS*$_S$)-4-*tert*-butylsulfinyl[2.2]paracyclophane (***RS***$_p$,***RS***$_S$)-**3**. To a solution of (±)-4-*tert*-butylsulfanyl[2.2]paracyclophane **5** (6.96 g, 23.51 mmol, 1.0 eq.) in CH_2Cl_2 (150 mL) at 0 °C was added *m*-chloroperbenzoic acid (72.5% in H_2O; 6.15 g, 25.86 mmol, 1.1 eq.) in several portions over a period of 15 min. After 1 hour the reaction mixture was poured into saturated aqueous $NaHCO_3$ (200 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography (2% diethyl ether in 60–80 petrol to 4% diethyl ether in 60–80 petrol) to give (***RS***$_p$,***RS***$_S$)-**3** as a crystalline solid (6.70 g, 91%); mp = 124–126 °C; ν_{max}/cm^{-1} 3054, 2987, 1422 and 1056; δ_H (300 MHz, $CDCl_3$) 7.01 (1H, d, J = 1.7 Hz, 5-H), 6.83 (1H, d, J = 8.1 Hz, 13-H), 6.63 (1H, dd, J = 7.8, 1.8 Hz, 7-H), 6.55 (1H, d, J = 8.4 Hz, 12-H), 6.52 (2H, br s, 15-H & 16-H), 6.48 (1H, d, J = 7.8 Hz, 8-H), 3.53 (1H, ddd, J = 13.1, 10.1, 2.8 Hz, 2-H), 3.27 (1H, ddd, J = 13.0, 9.9, 5.2 Hz, 1-H), 3.20–3.03 (5H, m, 1-H, 2 × 9-H, 2 × 10-H), 2.89 (1H, ddd, J = 13.5, 10.3, 5.5 Hz, 2-H), 1.05 (9H, s, *t*-Bu); δ_C (125 MHz, $CDCl_3$) 140.7 (C), 139.5 (C), 139.1 (C), 139.0, (C), 138.7 (C), 136.0 (CH), 134.6 (CH), 133.1 (CH), 132.7 (CH), 132.6 (CH), 132.3 (CH), 130.3 (CH), 56.6 (C), 35.2 (CH_2), 35.1 (CH_2), 34.7 (CH_2), 33.6 (CH_2), 22.7 (CH_3); HRMS (ESI) 335.1428 (MNa^+, $C_{20}H_{24}OSNa$ requires 335.1440).

§ *Crystallographic data* for (***RS***$_p$,***RS***$_S$)-**3**: $C_{20}H_{24}OS$, M = 312.45, T = 173(2) K, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 9.9320(5), b = 11.5642(6), c = 14.7502(4) Å, V = 1694.14(13) Å^3, Z = 4, D_c = 1.23 Mg m^{-3}, μ = 0.19 mm^{-1}, independent reflections = 2909 [R_{int} = 0.056], R_1 [for 2406 reflections with $I > 2\sigma(I)$] = 0.038, wR_2 (all data = 0.097). *Crystallographic data* for (***S***$_p$,***R***$_S$)-**3**: $C_{20}H_{24}OS$, M = 312.45, T = 173(2) K, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 9.9622(3), b = 11.5421(3), c = 14.9696(3) Å, V = 1721.28(8) Å^3, Z = 4, D_c = 1.21 Mg m^{-3}, μ = 0.19 mm^{-1}, independent reflections = 3022 [R_{int} = 0.068], R_1 [for 2694 reflections with $I > 2\sigma(I)$] = 0.040, wR_2 (all data = 0.100). CCDC reference numbers 278337–278338. See http://dx.doi.org/10.1039/b509994c for crystallographic data in CIF or other electronic format.

¶ Representative procedure. Synthesis of (*RS*$_p$,*RS*$_S$)-4-*tert*-butylsulfinyl-5-methyl[2.2]paracyclophane (***RS***$_p$,***RS***$_S$)-**8a**. To a solution of (*RS*$_p$,*RS*$_S$)-4-*tert*-butylsulfinyl[2.2]paracyclophane (***RS***$_p$,***RS***$_S$)-**3** (100 mg, 0.32 mmol, 1.0 eq.) in THF (6.0 mL) at 0 °C was added a solution of *n*-BuLi (2.5 in hexanes; 0.28 mL, 0.71 mmol, 2.2 eq.) dropwise over a period of 30 min. The resultant orange solution was stirred at 0 °C for a further 1 h, whereupon methyl iodide (0.08 mL, 1.28 mmol, 4.0 eq.) was added, instantly producing a yellow solution. The reaction mixture was warmed to room temperature overnight then poured into saturated aqueous NH_4Cl (20 mL) and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude residue was purified by column chromatography (1:2 diethyl ether:60–80 petrol to 4:1 diethyl ether:60–80 petrol) to give **8a** as a white powder (78.0 mg, 75%); mp = 149–151 °C; ν_{max}/cm^{-1} 3054, 2987, 1645, 1421, 1266 and 1037; δ_H (300 MHz, $CDCl_3$) 6.86 (2H, br s, 12-H & 13-H), 6.58 (1H, d, J = 7.7 Hz, 8-H or 7-H), 6.52 (1H, d, J = 7.6 Hz, 15-H or 16-H), 6.48 (1H, d, J = 8.1 Hz, 7-H or 8-H), 6.41 (1H, d, J = 7.7 Hz, 16-H or 15-H), 3.70 (1H, dd, J = 13.9, 11.1 Hz, 2-H), 3.38–3.21 (2H, m, 1-H & 1-H or 9-H), 3.17–3.00 (4H, m, 9-H or 1-H, 9-H & 2 × 10-H), 2.81–2.71 (1H, m, H-2), 2.47 (3H, s, CH_3), 1.14 (9H, s, *t*-Bu); δ_C (75 MHz, $CDCl_3$) 142.3 (C), 141.2 (C), 141.1 (C), 139.44 (C), 139.35 (C), 136.8 (CH), 134.3 (C), 133.4 (CH), 133.1 (CH), 133.0 (CH), 132.2 (CH), 128.6 (CH), 59.2 (C), 35.1 (CH_2), 34.6 (CH_2), 33.9 (CH_2), 33.0 (CH_2), 24.3 (CH_3), 16.0 (CH_3); HRMS (ESI) 349.1588 (MNa^+, $C_{21}H_{26}OSNa$ requires 349.1596).

‖ *Crystallographic data* for (***RS***$_p$,***RS***$_S$,***RS***)-**8i**: $C_{27}H_{30}O_2S$, M = 418.57, T = 173(2) K, triclinic, space group $P\bar{1}$, a = 10.8751(3), b = 13.6785(4), c = 16.9532(4) Å, α = 74.165(2)°, β = 75.054(2)°, γ = 69.839(1)°, V = 2239.71(10) Å^3, Z = 4, D_c = 1.24 Mg m^{-3}, μ = 0.17 mm^{-1}, independent reflections = 8788 [R_{int} = 0.0522], R_1 [for 6596 reflections with $I > 2\sigma(I)$] = 0.0448, wR_2 (all data = 0.109). *Crystallographic data* for (***RS***$_p$,***RS***$_S$,***RS***)-**8j**: $C_{24}H_{32}O_2S$, M = 384.56, T = 173(2) K, tetragonal, space group $P4_2/n$, a = 21.1744(9), b = 21.1744(9), c = 9.5008(6) Å, V = 4259.7(4) Å^3, Z = 8, D_c = 1.20 Mg m^{-3}, μ = 0.17 mm^{-1}, independent reflections = 2935 [R_{int} = 0.1631], R_1 [for 1767 reflections with $I > 2\sigma(I)$] = 0.0684, wR_2 (all data = 0.178). CCDC reference numbers 283984–283985. See http://dx.doi.org/10.1039/b509994c for crystallographic data in CIF or other electronic format.

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19 Preliminary results show that lithiation of enantiomer ($\boldsymbol{S}_p$,$\boldsymbol{R}_S$)-**3** does direct to C2, but at present the yield is not satisfactory; trapping the anion with benzaldehyde gives a 1:1 mixture of diastereoisomers in 30% yield. We are currently attempting to optimise this reaction.