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Synthesis of Novel C_2 Symmetrical and Enantiomerically Pure Thiepines

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Abstract Novel thiepines were synthesised using a Sharpless asymmetric dihydroxylation reaction to introduce the two chiral centres and with ring closure achieved by using sulfur diimidazole in conjunction with either a double *ortho*-lithiation or a double bromine/lithium exchange.
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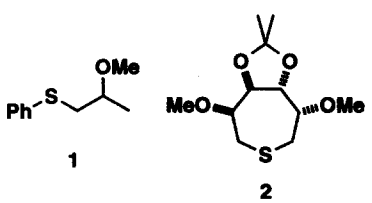
Both the synthesis and reactions of chiral sulfides are of interest to organic chemists; being used in migration reactions[1] and rearrangements.[2] Chiral sulfides which contain a prochiral sulfur atom have two diastereotopic sulfur lone pairs. Hence with sulfide **1**, alkylation leads to two diastereomeric products.[3] Diastereomers such as these may be difficult to separate and can react with different – even opposite – stereoselectivity.[4]

A chiral sulfide with a C_2 axis of symmetry and where that axis passes through the sulfur atom has homotopic, rather than diastereotopic, lone pairs and reaction of *either* lone pair leads to the same product.[5] Enantiomerically pure C_2 symmetrical sulfides have been prepared from D-mannitol (e.g. **2**)[6] and by using a resolution.[7] We report here the first enantioselective preparation of thiepine **4**[8] and the synthesis of new and enantiomerically pure C_2 symmetrical sulfides — thiepines **3** and **5** — together with the X-ray crystal structure of **3**.



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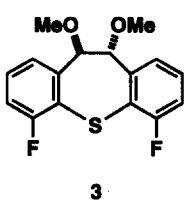

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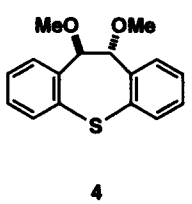

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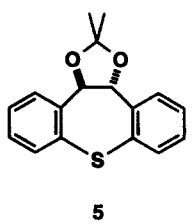

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Following our procedure[9] for the formation of diether **9** (Scheme 1), diol **8** was formed in 98% yield and >99% ee from 3,3'-difluorostilbene using the Sharpless AD mix-β. Hence the two chiral centres were installed in our molecule using a catalytic reagent based strategy. The enantiomeric purity of diol **8** was determined before recrystallisation using Pirkle's reagent[10, 11] and by chiral HPLC.[11, 12]

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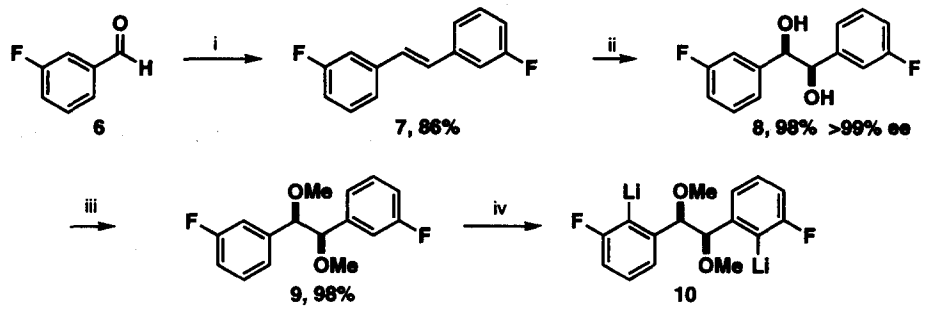
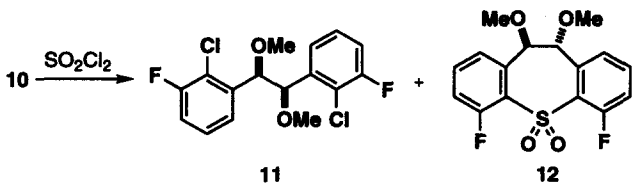


Scheme 1 *Reagents and conditions*: i, $TiCl_3$, Zn/Cu, DME reflux, 18 h; ii, AD-mix-β, 0-5 °C, 60 h; iii, NaH, THF, 0 °C ↑ room temp., then MeI, 0 °C ↑ room temp., 18 h; iv, *sec*-BuLi 2.5 eq., THF, –78 °C, 4 hr

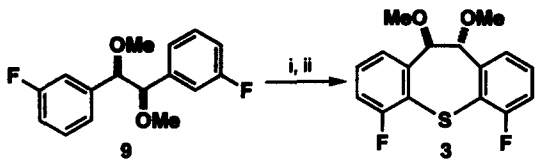
Diether **9** was then lithiated with *sec*-butyl lithium in THF at –78 °C to give the bislithiated compound **10**. The selectivity observed in the lithiation of **9** has been discussed and **10** used to form chiral phosphorus heterocycles†,[9] but otherwise the use of bislithiated compounds obtained by double *ortho*-lithiation is extremely rare.[13] Our plan was to form thiepine **3** by reacting **10** with a sulfur electrophile with two leaving groups. Initially we paid little attention to the oxidation state of the sulfur electrophiles we used since we were principally concerned with introducing, by any means, a sulfur atom. Attempts at using elemental sulfur gave sulfide **3** in approximately 10% yield. Sulfur dichloride, thionyl chloride and sulfuryl chloride were used in an attempt to make the sulfide, sulfoxide and sulfone respectively.[14] With sulfuryl chloride, we obtained a 19% yield of sulfone **12** but a 39% yield of the bischlorinated species **11** (Scheme 2). Thionyl chloride yielded only 8% of the sulfoxide **16** with **11** again being formed, but sulfur dichloride gave only a trace of sulfide **3**.



Scheme 2

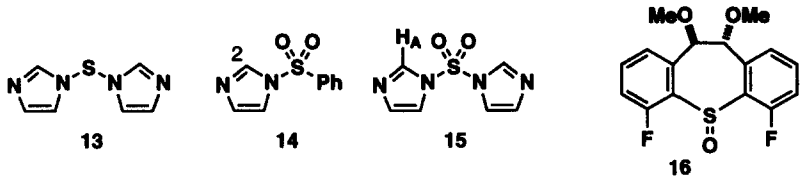
In order to improve the reaction, we reasoned that we might either alter the metal of our nucleophile or, given that the chlorine in the electrophile was causing the problem, change the electrophile for one without chlorine. Adopting the latter strategy, we decided to use sulfur diimidazole **13**. Sulfur diimidazole is conveniently prepared from trimethylsilylimidazole and sulfur dichloride by the method of Degen.[15] To the best of our knowledge, although sulfur diimidazole as been used in the formation of trisulfide linkages,[16] it has not been used in reactions with organolithium reagents before. In contrast to the chlorine atom, it seemed unlikely that the electron rich imidazole ring would undergo nucleophilic attack. Sulfur diimidazole was added as a suspension in THF to a solution of **10** and we were pleased to find that sulfide **3** was thus formed in a 46% yield (Scheme 3).

† These phosphorus heterocycles are not C_2 symmetric whereas the sulfides described are.

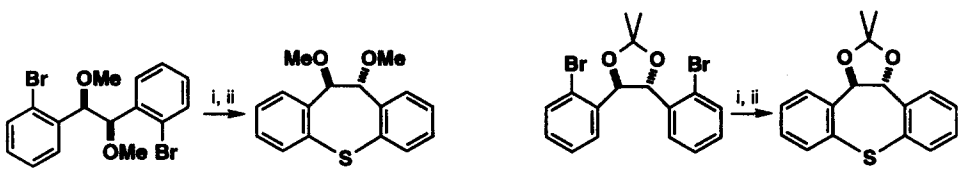


Scheme 3 *Reagents and conditions*: i, *sec*-BuLi 2.5 eq., –78 °C, THF, 4 hr; ii, **13** 5 eq., THF, –78 °C ↑ room temp. over night

Interestingly, both $SOIm_2$ and SO_2Im_2 **15** were completely ineffective as an electrophiles in reactions to form sulfoxide **16** or sulfone **12**. Instead starting material **9** was recovered in both cases. Given that benzenesulfonylimidazole **14** is known to lithiate at the 2-position,[17] we suspect that – if a reaction is occurring at all – proton H_A is removed from **15** by **10**. A similar situation probably arises with $SOIm_2$.



We have also synthesised thiepine **4** which does not have fluorine atoms on the benzene rings. Since the benzylic oxygen atoms like those of **9** are ineffective at directing an *ortho*-lithiation on their own, in this case the synthesis was achieved using a bromine/lithium exchange rather than a proton/lithium exchange of an *ortho*-lithiation.[18] The dibromide **17** was made by the same method as that used for difluoride **9**. Lithiation was achieved using *tert*-BuLi (two equivalents for each bromine) and sulfur diimidazole was again used as the sulfur electrophile. Sulfide **4** was formed in a 38% yield. Starting from dioxolane **18** we were, in a similar way, able to make thiepine **5** in an 18% yield.



Reagents and conditions: i, *tert*-BuLi 4 eq., THF, –78 °C ↑ –25 °C ↓ –78 °C; ii, **13** 5 eq. in THF, –78 °C ↑ room temp. over night

With both of these sulfides the chiral centres sit on the carbon backbone of the seven membered ring. This is quite a long way from the sulfur atom which will be the nucleophilic part of the molecule. However, we hope the chiral centres will induce a twist in the seven membered ring that will twist the two benzene rings relative to one another and hence translate chiral information from the back of the ring to the front. The proton NMR of **3** and **4** clearly shows that the molecules are symmetrical, but we can see from the X-ray crystal structure of **3** (Fig. 1) that it does not adopt a C_2 symmetrical conformation in the crystalline state.‡ In order to maintain a C_2 symmetric conformation in the crystalline state, the two benzene rings would need to twist about axis *x* (Fig. 2) — with the fluorine atom of one benzene ring moving above the plane and the fluorine atom moving below the plane with the other ring. However, the two benzene rings twist instead about axis *y* like the wings of a butterfly.

Chiral thiepines **3** and **4** differ from many other C_2 symmetrical sulfides in that they are diaryl sulfides. Compared to the lone pairs of other chiral sulfides, we expect the lone pairs on the sulfur atom of thiepine **4**, and especially those of thiepine **3**, to be really quite non-nucleophilic.[19] The synthetic strategy used for the synthesis of **3** and **4** is versatile in that it allows for variation of the alcohol protecting groups (hence **5**). It is here that variation is likely to influence the conformation of the seven-membered ring. The applications of these sulfides are now being investigated in our laboratory.

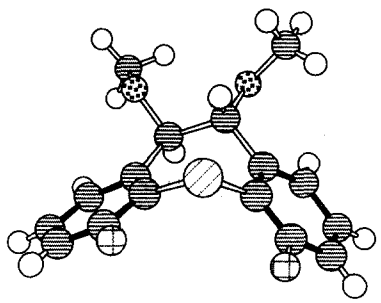


Fig. 1 X-Ray Crystal structure of **3**

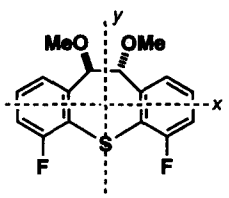


Fig. 2

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Notes and References

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‡ Crystal data for **3** — Single crystals of **3** were grown from petroleum ether (bp 40-60 °C). $C_{16}H_{14}F_2O_2S$, M = 308.34, orthorhombic, a = 7.839(2) Å, b = 11.645(2) Å, c = 15.476(2) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, V = 1412.7(4) Å^3, T = 173(2) K, space group $P2_12_12_1$, Z = 4, μ = 0.253 mm^{-1}; 9132 reflections collected, 3223 [R(int) = 0.0336] independent reflections, R_1 = 0.0264 [I>2σ(I)], wR_2 = 0.0652.

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