Synthesis and chemistry of enantiomerically pure 10,11-dihydrodibenzo[*b*,*f*]thiepines

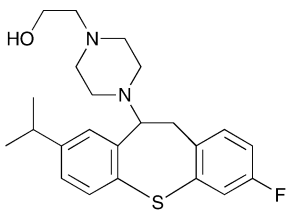
Paul Wyatt,* Andrew Hudson, Jonathan Charmant, A. Guy Orpen and Hirihattaya Phetmung

Received 23rd November 2005, Accepted 14th March 2006
First published as an Advance Article on the web 3rd May 2006
DOI: 10.1039/b516606c

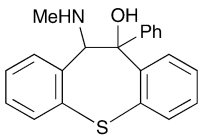
Several chiral thiepines were efficiently constructed using sulfur diimidazole in combination with a variety of bislithiated carbon fragments. The sulfur atom in these thiepines is found to be unusually unreactive compared to diphenylsulfide.

Introduction

The dibenzothiepine is an important substructure within many biologically active compounds. These include isofloxythiepine which is a potent neuroleptic[1] and thiepine **1**, which has shown promising antidepressant activity.[2] We have communicated the synthesis of optically pure seven membered sulfur heterocycles – thiepines.[3] We now report the synthesis of a variety of thiepines in full as well as reactions that were attempted with these compounds.

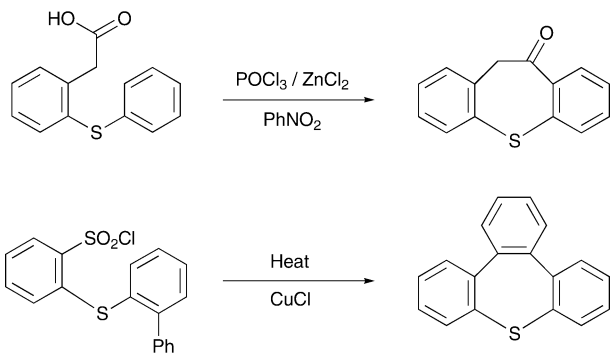


isofloxythiepine



1

There are several methods for the formation of thiepines and many include a carbon–carbon bond formation in the ring forming step. Hence an intramolecular acylation reaction[4] or double Knovenagel condensation[5] have been used (Scheme 1) as has ring expansion[6] and other methods.[7] Our strategy involves the formation of a carbon–sulfur bond in the ring forming step with *both* carbon–sulfur bonds being made in the same reaction (see Scheme 4).

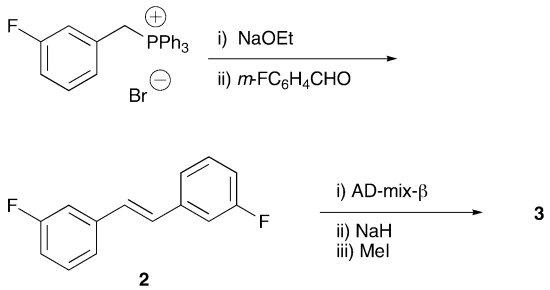


Scheme 1 Formation of thiepines.

School of Chemistry, Cantock's Close, Bristol, UK BS8 1TS

Synthesis

The strategy for the synthesis of thiepines is the same as that used in the synthesis of corresponding phosphepines.[8] The syntheses of compounds **3** to **8** have been reported before in that context. In brief, the overall synthesis involves the formation of a stilbene such as difluorostilbene **2** which is then dihydroxylated, protected (Scheme 2) and a double lithiation performed before ring closure on electrophilic sulfur (see Scheme 4). The only carbon–carbon bond formed in the synthesis is in making the stilbenes.



Scheme 2

We have previously used low-valent titanium made from $TiCl_3$ for this step[9] and have also used the combination of titanium powder and trimethylsilyl chloride,[10] but a much more convenient and cost-effective method was a medium-scale Wittig reaction.[11] The only poor Wittig reaction was in the formation of the tetrafluorinated stilbene (which was reacted on to diether **11**) which was formed in only 21% yield. The equilibration of the mixture of *cis*- and *trans*-stilbenes into *trans*-stilbene was achieved using iodine and sunlight and proved most convenient.† We were thus able to make *trans*-stilbenes in 40 gram batches.

Compounds **3–11** were prepared by standard methods from the corresponding diols with a view to constructing a range of thiepines (Fig. 1).

Lithiation of compounds

The lithiation of the compounds was achieved using either halogen–lithium exchange or *ortho*-lithiation. The excellent regio-selection of difluoride **3** at the 2-position rather than the 4-position was reflected in the lithiation of the related MOM ether

† The one day of equilibration noted in the reference referred to Californian sunlight which translated to seven days of sunlight in Bristol.

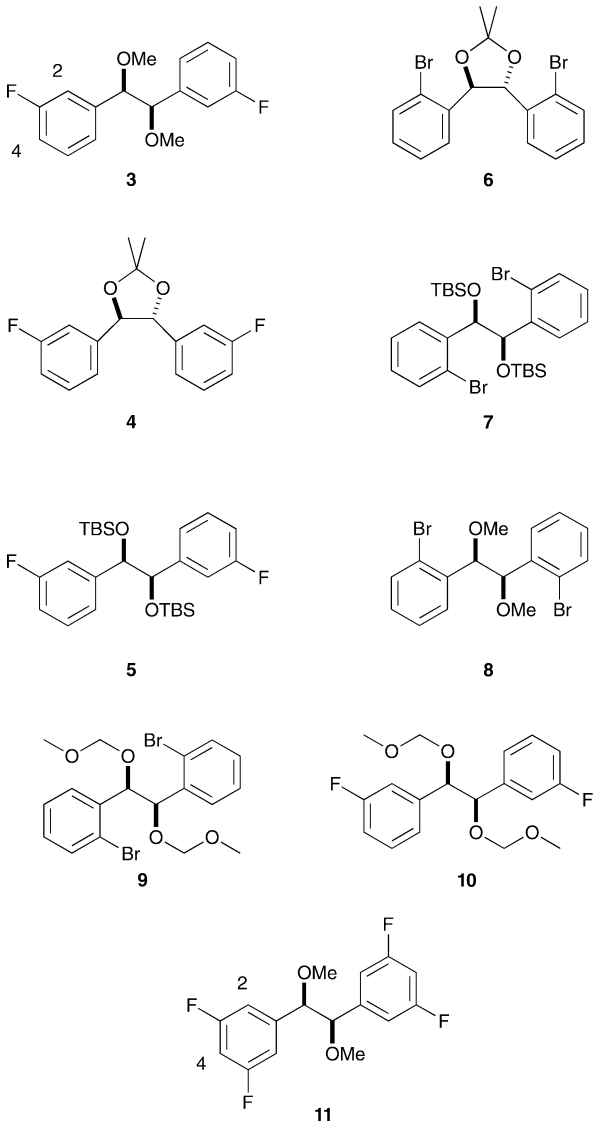
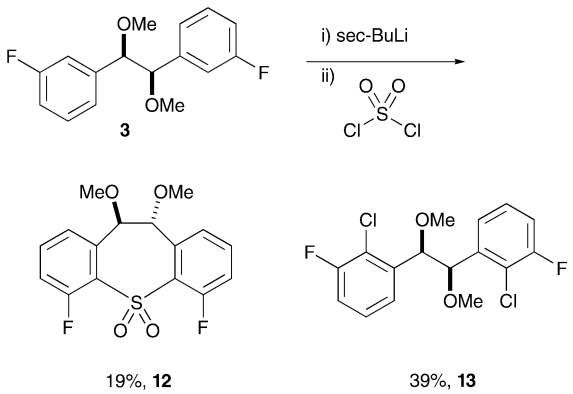


Fig. 1 Substrates for lithiation.

10. This regioselection was also present with the acetal **4** and silyl ether **5** however, although the degree of bislithiation of diether **3** was 96% (an improvement over the previously-reported 84%) it was 43% with silyl ether **5** and only 6% with acetal **4**. Unsurprisingly, lithation of the tetrafluorinated diether **11** was completely regioselective for the 4-position (instead of the 2-position) and was not useful for ring synthesis. The degree of lithiation was detected in each case by quenching with methyl iodide and analysing the degree and position of methylation. Hence lithiation is at least as good as the figures indicated above because methylation, although excellent, will not be quantitative. All the bromine containing compounds (**6–9**) were lithiated with four equivalents of *tert*-butyl lithium (two per reactive site) and lithiated as expected.

The sulfur transfer reagent

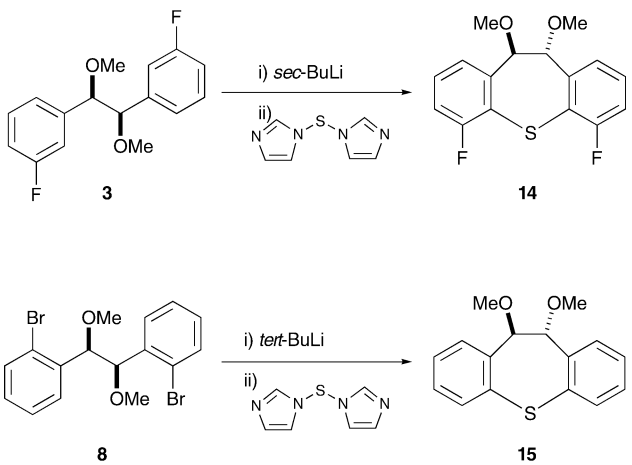
During the early stages of the work we were concerned with introducing sulfur by any means possible and at any oxidation level. Experiments were conducted using the compound which was most reliable when it came to lithiation – diether **3**. The usual suspects of elemental sulfur, thionyl chloride, sulfuryl chloride and SCl_2 itself were tried. Although elemental sulfur did work to a degree, giving the desired product in 10% yield, it also gave rise to a host of other compounds and this lack of selectivity meant it was not a useful reagent. Of all these reagents, the least bad results were obtained with sulfuryl chloride which gave sulfone **12** in 19% yield (Scheme 3).



Scheme 3

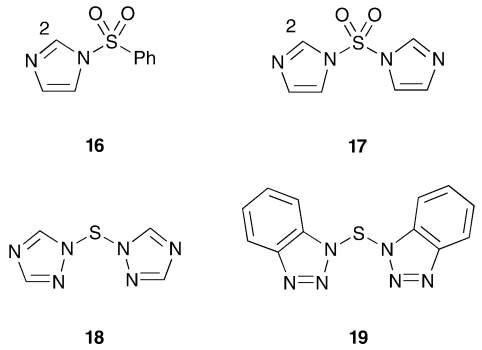
The main by-product was the chlorinated diether **13** (39% yield). Given that sulfuryl chloride is a chlorinating agent this was scarcely a surprise but it set us on the road to success. Clearly a chloride leaving group was not suitable and we moved to using an imidazole anion as the leaving group.

Sulfur diimidazole was readily prepared by the method of Degen by the combination of SCl_2 and TMSimidazole.[12] The SIm_2 precipitates from hexane solution and could be washed with hexane and then used immediately as a solution in THF. It is not especially soluble and so for larger scale reactions it was added as a fine suspension in THF. We were pleased to find reaction of lithiated **3** with SIm_2 gave the thiepine **14** in 48% yield (Scheme 4). Given the success of sulfuryl chloride over sulfur chloride we also prepared SO_2Im_2 (**17**) and $SOIm_2$ but, in reaction with lithiated **3**, these electrophiles gave us only starting material **3**. If there is a reaction at all with these two electrophiles perhaps the proton at



Scheme 4

position-2 is being removed – after all, benzenesulfonylimidiazole (**16**) lithiates at this position (Fig. 2).[13]

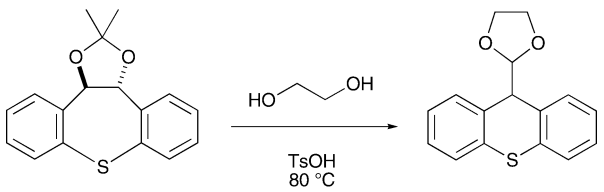


16 **17** **18** **19**

Fig. 2 Alternative reagents to sulfur diimidazole.

In trying to improve on sulfur diimidazole as a way to introduce sulfur, we investigated similar reagents (made in the same way as SIm_2) but matters were not improved using sulfur ditriazole **18** (21% yield of thiepine **14**) or sulfur bisbenzotriazole **19** (11% yield). Hence we settled upon SIm_2 as the reagent for all other thiepine formation reactions. Using SIm_2 a total of six novel chiral thiepines from precursors **3** and **6–10** were prepared (Table 1).

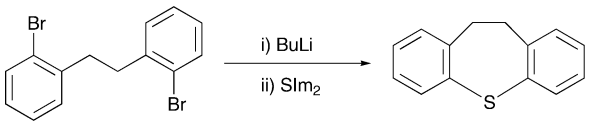
Interestingly, treatment of thiepine **22** with a combination of ethylene glycol and tosic acid (in an attempt to remove the acetal function) allowed entry into the pharmaceutically important thioxanthene ring system **24**.[14] The mechanism presumably involves a 1,2-sigmatropic shift to contract the seven membered ring with the resulting aldehyde being trapped by the ethylene glycol.



22 **24**, 68%

Formation of achiral thiepines

We imagined, incorrectly as it turned out, that the achiral thiepine **26** would be easy to synthesise and serve as a useful model for reactions of its chiral counterpart. In fact, we were to find that the behaviour of the precursor to the achiral thiepine (**25**) and precursors to chiral thiepines (**8** and **3**) was radically different.



25 **26** <3%

Reaction of lithiated bibenzyl **25** with sulfur diimidazole gave only a 3% yield of simple thiepine **26**. And this was on the best occasion – usually it gave no thiepine at all. Given the success of SIm_2 with the other substrates we found this extraordinary; particularly when heterocycles with other electrophiles have been made with this substrate.[15] However, the result was entirely reproducible. It is fortunate that we obtained this negative result *after* we had already done a successful reaction with a chiral substrate. It would have been tempting indeed to conclude that SIm_2 was ineffective as a double sulfur electrophile for use with organolithium reagents and abandoned it. We were to find on other occasions that the reactivity of dibromide **25** did not mimic the reactivity of chiral dibromides in the least.

NMR spectra

Thiepine **14** is C_2 symmetrical and this is evident in the NMR spectrum – a singlet is visible for the two benzylic protons and for the two methyl groups. This symmetry is destroyed upon oxidation to the sulfoxide. The difference in chemical shift between the two diastereotopic benzylic protons of the sulfoxide is remarkable. To the uninitiated it might appear that the expected AB quartet is missing. In fact one of the doublets is so far downfield it masquerades as an aromatic signal (Fig. 3).

The X-ray crystal structure of thiepine **14** has been revealed before.[3] The two benzene rings are not in the same plane but angled so as to form a 'butterfly' arrangement (Fig. 4). They are twisted so that (viewed from the sulfur atom) we see one leading edge is slightly above the other. The anti-periplanar nature of the two homotopic benzylic protons can also be seen. From the ^{13}C satellite peaks detected in the ^{1}H NMR spectrum we found the coupling

Table 1 New thiepines

Starting material	R^1	X	Equivalents of butyl lithium	E	Y	Yield	Compound
3	Me	3-F	2.2eq *sec*-BuLi	SIm_2	4,6-F	48%	**14**
3	Me	3-F	2.2eq *sec*-BuLi	SCl_2	4,6-F	3%	**14**
10	OCH_2OMe	3-F	2.36 eq *sec*-BuLi	SIm_2	4,6-F	37%	**20**
8	Me	2-Br	4 eq *tert*-BuLi	SIm_2	H	38%	**15**
7	$SiMe_2{}^tBu$	2-Br	4 eq *tert*-BuLi	SIm_2	H	19%	**21**
6	CMe_2	2-Br	4 eq *tert*-BuLi	SIm_2	H	12%	**22**
9	OCH_2OMe	2-Br	4 eq *tert*-BuLi	SIm_2	H	36%	**23**

Reagents and conditions: i, conditions in Table 1; ii, SIm_2.

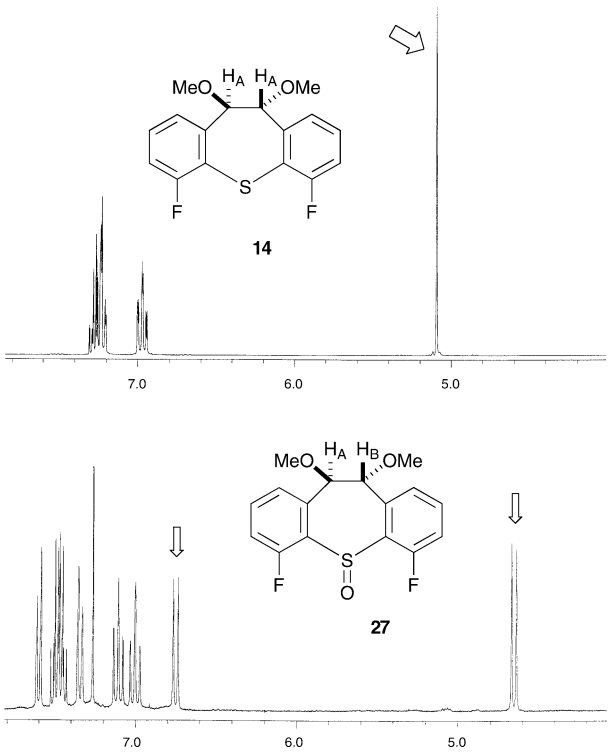


Fig. 3 Detail of two NMR spectra contrasting homotopic and diastereotopic signals from benzylic protons.

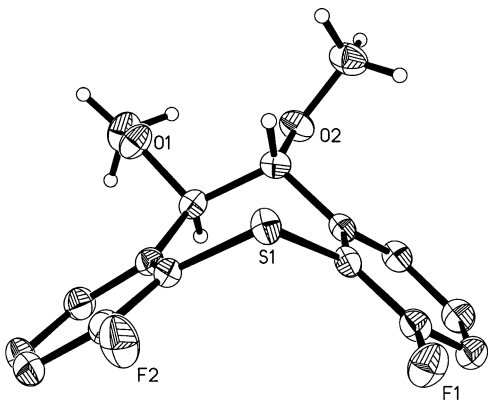


Fig. 4 ORTEP drawing of thiepine **14**; 50% probability ellipsoids.‡

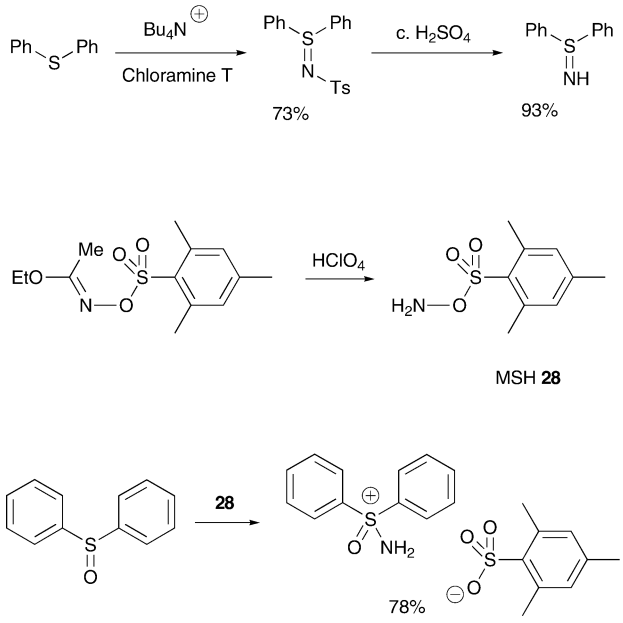
constant between these hydrogen atoms was 8.6 Hz. With sulfoxide **27**, a view from the front (S=O to backbone, Fig. 5a) shows a slightly more pronounced butterfly arrangement and a view from the side (Fig. 5b) shows how the S=O bond bends back across the seven membered ring and is in reasonably close proximity (2.3 Å) to one of the benzylic hydrogen atoms but not the other (which is on the other side of the ring). This accounts, perhaps, for the dramatically different environments of the diastereotopic protons. Fig. 5 shows only one of the two independent molecules of sulfoxide **27**.

‡ Crystal data for (−)-**14**. Single crystals of **14** 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 $P2_12_12_1$, $Z = 4$, $\mu = 0.253$ mm^{-1}; 9132 reflections collected, 3223 [$R_{int} = 0.0336$] independent reflections, $R_1 = 0.0264$ [$I > 2\sigma(I)$], $wR_2 = 0.0644$. With a Flack parameter of 0.02(6), the absolute stereochemistry is clearly established and is in accord with the configuration of the starting material. CCDC reference number 290626. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b516606c

Reactivity of the thiepines

Because the thiepines are C_2 symmetrical, the two lone pairs on the sulfur atom are homotopic and there is thus no concern over the formation of diastereomers in any reaction. A reaction of thiepine **14** that could be conducted readily was its oxidation to sulfoxide **27**. This was done in quantitative yield with mCPBA. Usually, the oxidation of sulfides to sulfoxides has to be conducted carefully to avoid over-oxidation to the sulfone.[16] This was not the case here – sulfoxide **27** could not be oxidized to the sulfone even under the most forcing conditions. This lack of reactivity was a taste of things to come as the sulfur atom of thiepine **14** was to prove remarkably unreactive and known reactions of Ph_2S, which we could repeat with ease, failed. Since most of our first reactions were conducted with thiepine **14**, we initially considered that this might be due to the electron-withdrawing nature of the fluorine atoms. However, reactivity was not improved with the analogous thiepine **15**.

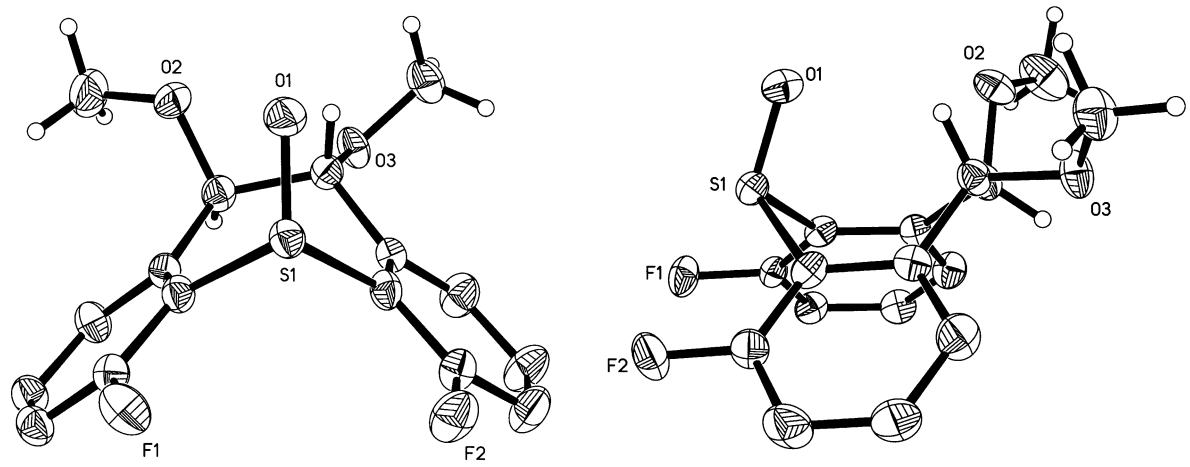
Yamamoto's tetrabutylammonium salt of chloramine T§,[17] worked nicely for us to turn diphenyl sulfide into its corresponding tosylsulfimide. When this was treated with concentrated H_2SO_4, the free sulfimide was produced in 93% yield (Scheme 5).[18] However reaction of thiepine **15** and the salt of chloramine T was not successful. Either there was no reaction at all or, under more forcing conditions, destruction of the thiepine. It was a similar story for the reaction of thiepine **15** with PhI=NTs in the presence of CuOTf.[19,20] Methylation failed with MeOTf,[21] MeI/$AgBF_4$[22] or Me_3OBF_4.[23]



Scheme 5 Reactions of Ph_2S and Ph_2SO that fail with thiepines.[24,25]

Mesitylenesulfonylhydroxylamine (MSH) **28** was prepared from ethyl (*O*-mesitylenesulfonyl)acetohydroxamate (Scheme 5).[24]

§ Reaction with normal chloramine T fails.

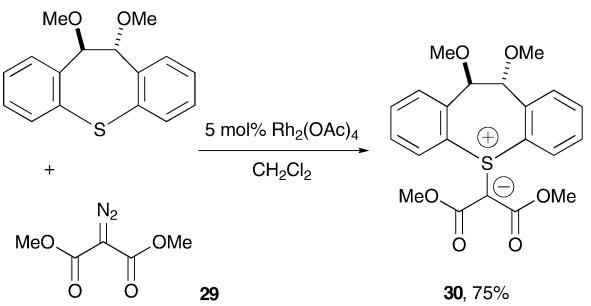


a. View sulfur to backbone *b. Sideview*

Fig. 5 ORTEP drawings of thiepine oxide **27**; 50% probability ellipsoids.¶

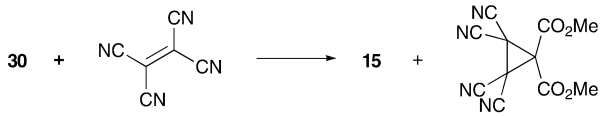
Diphenyl sulfoxide reacted with MSH **28** to give the aminated product in 78% yield[25] (Scheme 5) but thiepine oxide **27** did not react.

The reaction of sulfides with diazo compounds to give sulfonium ylides directly is a well known process and, with electron withdrawing groups present to stabilise the negative charge, these ylides can be stable isolable compounds.[26, 27] Dimethyldiazomalonate **29** was prepared by the reaction of dimethylmalonate with sodium azide. Thiepine **15** was reacted with the diazomalonate in the presence of 5% $Rh_2(OAc)_4$ to give ylide **30** in 75% yield (Scheme 6). The ylide could be purified by column chromatography. Thiepine **15** also reacted with dibenzyldiazomalonate under the same conditions to give the corresponding ylide (**32**) in 63% yield.



Scheme 6

The ylide was stable to reflux conditions in dichloromethane or toluene for several days. Unfortunately, the reactivity of the stabilised sulfonium ylide is very limited and restricted to exceptional Michael acceptors (unsurprisingly, the ylide failed to react with benzaldehyde or dicyanoethylene). Reaction with tetracyanoethylene lead to the consumption of the ylide. Thiepine **15** was produced in the reaction and the formation of cyclopropane **31** suggested.[28]



31

Conclusions

Although sulfur diimidazole has been used a great deal for the construction of, for instance, symmetrical trisulfides[29] it has not previously been reported as a reagent in combination with organolithium reagents. Clearly it is a very suitable reagent for such reactions. The chiral thiepines we have investigated have very unreactive sulfur atoms and we thus turned our attention to the chiral disulfides[30] (dithiocines) and trisulfides (trithionines) that could be made using the same carbon backbone. Our findings in this area will be reported in due course.

Experimental

General

Flash chromatography was performed using Merck 9385 Kieselgel 60 according to Still *et al.*[31] Thin layer chromatography (TLC) was performed using commercially available glass plates coated with Merck silica Kieselgel $60F_{254}$. The compounds were visualised by a Mineralight UV lamp or by dipping into a potassium permanganate solution in aqueous sodium hydroxide and heating with a hot air gun. High performance liqiud chromatography (HPLC) was performed using a Dynamax prepacked silica column (25 cm × 21.4 mm internal diameter), a Gilson model 303 pump and a Dynamax Rainin UV detector at 254 nm.

Melting points were determined on a Gallenkemp melting point apparatus and are uncorrected. Infra red spectra were recorded on a Perkin Elmer 141 spectrophotometer as liquid films or as solutions in dichloromethane on sodium chloride plates. Optical

¶ Crystal data for (−)-**27**. Single crystals were grown from petroleum ether (bp 40–60 °C). $C_{16}H_{14}F_2O_3S$, $M = 324.33$, triclinic, $a = 7.986(3)$ Å, $b = 8.7928(16)$ Å, $c = 11.254(3)$ Å, $\alpha = 89.389(19)°$, $\beta = 82.07(2)°$, $\gamma = 67.49(2)°$, $V = 722.3(4)$ Å^3, $T = 173(2)$ K, space group $P1$, $Z = 2$, $\mu = 0.256$ mm^{-1}; 7358 reflections collected, 5913 [$R_{int} = 0.0289$] independent reflections, $R_1 = 0.0432$ [$I > 2\sigma(I)$], $wR_2 = 0.0912$. With a Flack parameter of −0.06(9), the absolute stereochemistry is clearly established and is in accord with the configuration of the starting material. CCDC reference numbers 290627. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b516606c

rotations were recorded on a Perkin Elmer 241 MC polarimeter irradiating with the sodium D line ($\lambda = 589$ nm) and $[\alpha]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}.

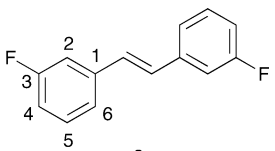
All nuclear magnetic resonance (NMR) spectra were recorded as solutions using tetramethylsilane as the internal reference on a Jeol GX270 MHz, GX400 MHz or λ300 MHz spectrometer.

All mass spectra were recorded on a Fisons Autospec mass spectrometer and were determined by electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) techniques.

When using alkyl lithium reagents, best results were obtained using Hamilton 1700 series gas-tight Teflon tipped microsyringes (<1000 μl), which did not require lubrication, and Hamilton 1700 series gas-tight Teflon tipped syringes (>1 ml) lubricated with poly(dimethylsiloxane) 200 ® fluid with a viscosity of 100 centistokes. All solvents were distilled before use; dry solvents were purchased from Fluka. Distilled 40–60 °C petroleum ether was used for flash chromatography and distilled 60–80 °C petroleum ether for recrystallisations.

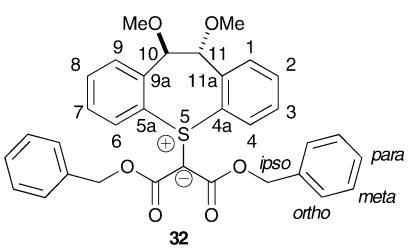
Key to assignments

The notation used for aromatic protons and carbon assignments is as follows: aromatic protons are referred to by their ring position followed by "-ArH". An illustration is provided with 3,3′-difluorostilbene **2** (Fig. 6). The proton which is *meta* to both fluorine and the olefinic substituent is referred to as 5-ArH. Aromatic carbons are referred to in a similar manner. The carbon assignment for difluorostilbene **2** (Fig. 7) is: 163.1 ($^1J_{CF}$ 246.6, 3-ArC), 139.2 ($^3J_{CF}$ 8.1, 1-ArC), 130.2 ($^3J_{CF}$ 8.7, 5-ArC), 128.8 ($^4J_{CF}$ 2.5, Ar*C*H), 122.6 ($^4J_{CF}$ 2.5, 6-ArC), 114.8 ($^2J_{CF}$ 21.1, 2-ArC) and 112.9 ($^2J_{CF}$ 17.2, 4-ArC). The "C" in "ArC" is the numbered carbon within that ring and not a carbon attached to the ring. Carbons outside the ring are italicised when "Ar" is included in the assignment *e.g.* 78.4 ($^4J_{CF}$ 1.2, Ar*C*H). If there is possible ambiguity as to which proton or carbon the assignment refers to the appropriate atom is italicised. When a carbon nucleus is observed to couple to one other nucleus then it is not referred to as a doublet. Any greater multiplicity is noted. In some cases quaternary carbons were not observed in the ^{13}C-NMR spectrum and hence have not been included in the assignment.



2

Fig. 6 Difluorostilbene assignments.



32

Fig. 7 Thiepine assignments.

Protons and carbons which form part of a ring system are numbered according to the numbering system indicated in Fig. 7. The *exo*-cyclic portion is assigned using the labels *ipso*, *ortho*, *meta* and *para.* In an instance when a compound contains an *exo*-cyclic ring and it is clear which portion an atom belongs to, but not the exact position, then the label *exo* is used in the assignment. In addition if the spectroscopic data relating to, for example, positions "1" and "9" are homotopic or enantiotopic (Fig. 7), only position "1" is denoted in the assignment.

When coupling constants refer to the coupling between two protons, or between two unassigned nuclei, then no subscripts follow "*J*". In NMR spectra of mixtures of compounds, peaks assignable to each compound are denoted. All solids were white and all oils colourless unless otherwise stated.

Stilbenes

(3-Fluorobenzyl)triphenylphosphonium bromide. 3-Fluorobenzyl bromide (19.5 ml, 0.159 mol) was dissolved in DMF (87 ml). Triphenylphosphine (45.8 g, 0.175 mol) was added to the solution and the reaction vigorously stirred at room temperature overnight. The mixture was poured into toluene (200 ml) and the suspension filtered. The solid product was dissolved in dichloromethane (150 ml) and reprecipitated by the addition of diethyl ether (200 ml). The precipitate was isolated by vacuum filtration to yield the phosphonium salt as a fine powder (66.3 g, 92.6%); mp >250 °C (lit.,[32] mp 309–310 °C); δ_H(300 MHz; DMSO) 7.96–7.89 (3 H, m, ArH), 7.81–7.68 (12 H, m, ArH), 7.36–7.26 (1 H, m, ArH), 7.20–7.11 (1 H, m, ArH), 6.91–6.75 (2 H, m, ArH) and 5.34 (2 H, d, $^2J_{PH}$ 15.9, ArC*H*); *m*/*z* (FAB) 371 (M^+, 100%).

***E*-3,3′-Difluorostilbene 2.** Sodium metal (1.12 g, 48.7 mmol) dissolved in dry ethanol (50 ml) was added to (3-fluorobenzyl)-triphenylphosphonium bromide (20.0 g, 44.3 mmol) in dry ethanol (150 ml) under an argon atmosphere. After the exothermic reaction was complete the solution was allowed to cool to room temperature and was then added dropwise to the phosphonium suspension. The mixture was warmed to 40 °C and stirred at this temperature for 0.5 h to produce a deep orange solution. After allowing the reaction mixture to cool to room temperature 3-fluorobenzaldehyde (4.70 ml, 44.3 mmol), dissolved in dry ethanol (40 ml), was added dropwise to the solution. The reaction was heated to reflux and stirred at this temperature for 0.5 h and then allowed to cool to room temperature before the dropwise addition of concentrated hydrochloric acid (30 ml). The solution was concentrated under reduced pressure, water (50 ml) was added and the mixture extracted with toluene (3 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with petroleum ether, to yield a colourless oil.

The oil was dissolved in hot heptane (100 ml) to which a few small crystals of iodine were added until a strong violet colour remained. The solution was exposed to direct sunlight for seven days during which time the solid product crystallised out of the solution. The suspension was filtered and the crystals washed with heptane (50 ml). The residue was purified by flash chromatography, eluting with petroleum ether, and recrystallised from petroleum ether to yield the *trans*-stilbene as needles (6.93 g,

72.4%). This compound was also made by McMurry coupling (methods **A** and **B**).

Method A. Anhydrous 1,2-dimethoxyethane (350 ml) was added to titanium(III) chloride (25.0 g, 0.162 mol) under an argon atmosphere. The suspension was heated to reflux and stirred at this temperature for 1.5 h, the reaction was vigorously mixed throughout using an overhead mechanical stirrer. The suspension was allowed to cool to room temperature before dry copper sulfate (3.10 g, 4.88 mmol) and zinc powder (40.7 g, 0.623 mol) were added, the reaction heated to reflux and the suspension was stirred at this temperature for a further two days. The reaction was allowed to cool to room temperature, 3-fluorobenzaldehyde (4.29 ml, 40.5 mmol) was added and the reaction heated to reflux and stirred at this temperature for 18 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (3 × 200 ml), filtered through a pad of Florisil and concentrated under reduced pressure. The solid residue was dissolved in dichloromethane and passed through silica. Recrystallisation from petroleum ether yielded the *trans*-stilbene as hexagonal plates (3.77 g, 86.2%); mp 86–87 °C (from petroleum ether) (lit.,[8] mp 86–87 °C); δ_H(300 MHz; $CDCl_3$) 7.33 (2 H, td, *J* 7.8 and $^4J_{HF}$ 5.7, 5-ArH), 7.27 (2 H, dt, *J* 7.8 and 1.4, 6-ArH), 7.21 (2 H, ddd, $^3J_{HF}$ 7.8, *J* 2.5 and 1.4, 2-ArH), 7.06 (2 H, s, ArC*H*) and 6.98 (2 H, tdd, $^3J_{HF}$ 7.8, *J* 7.8, 2.5 and 1.4, 4-ArH); δ_C(75.5 MHz; $CDCl_3$) 163.1 ($^1J_{CF}$ 246.6, 3-ArC), 139.2 ($^3J_{CF}$ 8.1, 1-ArC), 130.2 ($^3J_{CF}$ 8.7, 5-ArC), 128.8 ($^4J_{CF}$ 2.5, Ar*C*H), 122.6 ($^4J_{CF}$ 2.5, 6-ArC), 114.8 ($^2J_{CF}$ 21.1, 2-ArC) and 112.9 ($^2J_{CF}$ 17.2, 4-ArC).

Method B. Anhydrous 1,2-dimethoxyethane (350 ml) was added to titanium powder (21.8 g, 0.454 mol) under an argon atmosphere. Trimethylsilyl chloride (19.3 ml, 0.152 mol) was added to the suspension, the reaction heated to reflux and vigorously stirred for five days at this temperature using an overhead mechanical stirrer. 3-Fluorobenzaldehyde (4.29 ml, 40.5 mmol) was added to the suspension under reflux and the reaction stirred at this temperature for a further 3 h. The suspension was allowed to cool to room temperature. The same work up as previously described in method A yielded the *trans*-stilbene as hexagonal plates (4.84 g, 55.3%).

(3,5-Difluorobenzyl)triphenylphosphonium bromide. 3,5-Difluorobenzyl bromide (10.0 g, 48.3 mmol) was reacted in a method similar to that used in the synthesis of (3-fluorobenzyl)-triphenylphosphonium bromide. The product was dried under vacuum to yield the *phosphonium salt* as a fine powder (22.4 g, 98.8%); mp >250 °C δ_H(300 MHz; $CDCl_3$) 7.97–7.90 (5 H, m, PPh_3), 7.82–7.70 (10H, m, PPh_3), 7.26 (1 H, tdd, $^3J_{HF}$ 8.7, *J* 4.7 and 2.3, 4-ArH), 6.70–6.64 (2 H, m, 2-ArH) and 5.27 (2 H, d, $^2J_{PH}$ 16.0, ArC*H*); δ_C(67.9 MHz; $CDCl_3$) 162.7 (dd, $^1J_{CF}$ 247.3 and $^3J_{CF}$ 4.1, 3 or 5-ArC), 135.9 ($^4J_{CP}$ 2.6, *para*-ArC), 134.6 ($^3J_{CP}$ 10.4, *meta*-ArC), 132.9 (dd, $^2J_{CP}$ 18.3 and $^3J_{CF}$ 8.2, 1-ArC), 130.8 ($^2J_{CP}$ 12.3, *ortho*-ArC), 117.8 ($^1J_{CP}$ 86.2, *ipso*-ArC), 114.9 (m, 2-ArC) and 104.7 (t, $^2J_{CF}$ 21.1, 4-ArC) and 27.5 ($^1J_{CP}$ 86.2, Ar*C*H); δ_F(282.65 MHz, $CDCl_3$) −108.7 (t, $^3J_{HF}$ 8.7); δ_P(121.6 MHz, $CDCl_3$) 23.8; *m*/*z* (FAB) 389 (M^+, 100%).

***E*-3,3′,5,5′-Tetrafluorostilbene and *Z*-3,3′,5,5′-tetrafluorostilbene.** (3,5-Difluorobenzyl)triphenylphosphonium bromide (21.0 g, 44.7 mmol) was reacted with 3,5-difluorobenzaldehyde (5.82 g, 40.7 mmol) in a method similar to that used in the synthesis of stilbene **2**. No attempt was made to isomerise the *E* : *Z* mixture. The crude product was purified by flash chromatography, eluting with petroleum ether, and recrystallised from petroleum ether to yield the *trans-stilbene* as needles (1.29 g, 11.4%); mp 133.5–135 °C (from petroleum ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 1624 (Ar), 1600 (Ar) and 1456 (Ar); δ_H(300 MHz; $CDCl_3$) 6.74–6.62 (6 H, m, ArH) and 6.66 (2 H, s, ArC*H*); δ_C(75.5 MHz; $CDCl_3$) 163.1 (dd, $^1J_{CF}$ 248.2 and $^3J_{CF}$ 13.0, 3-ArC), 139.5 (t, $^3J_{CF}$ 9.9, 1-ArC), 130.3 (t, $^4J_{CF}$ 2.5, Ar*C*H), 111.7 (dd, $^2J_{CF}$ 17.4 and $^4J_{CF}$ 8.1, 2-ArC) and 103.2 (t, $^2J_{CF}$ 25.4, 4-ArC); δ_F(282.65 MHz, $CDCl_3$) −109.5 (t, $^3J_{HF}$ 8.2); *m*/*z* (CI) 253.0633 (MH^+. $C_{14}H_8F_4$ requires 253.0640), 252 (MH^+ − H, 100%), 233 (MH^+ − HF, 31) and 127 ($ArCH_2$, 22); and the *cis-stilbene* as fine needles (1.07 g, 9.5%); mp 114–114.5 °C (from heptane); $\nu_{max}(CHCl_3)/cm^{-1}$ 1623 (Ar) and 1597 (Ar); δ_H(300 MHz; $CDCl_3$) 7.02–6.99 (4 H, m, ArH), 6.99 (2 H, s, ArC*H*) and 6.74 (2 H, tt, $^3J_{HF}$ 8.7 and *J* 2.2, 4-ArH); δ_C(75.5 MHz; $CDCl_3$) 163.3 (dd, $^1J_{CF}$ 247.6 and $^3J_{CF}$ 13.1, 3-ArC), 139.7 (t, $^3J_{CF}$ 9.4, 1-ArC), 129.0 (Ar*C*H), 109.4 (dd, $^2J_{CF}$ 17.4 and $^4J_{CF}$ 8.1, 2-ArC) and 103.5 (t, $^2J_{CF}$ 26.0, 4-ArC); δ_F(282.65 MHz, $CDCl_3$) −109.6 (t, $^3J_{HF}$ 8.7); *m*/*z* (EI) 252.0565 (M^+. $C_{14}H_8F_4$ requires 252.0565) and 232 (M^+ − HF, 51%).

(2-Bromobenzyl)triphenylphosphonium bromide. 2-Bromobenzyl bromide (96.3 g, 0.385 mol) was reacted in a method similar to that used in the synthesis of (3-fluorobenzyl)-triphenylphosphonium bromide. The product was dried under vacuum to yield the phosphonium salt as a fine powder (186 g, 94.3%); mp 163–168 °C (from diethyl ether) (lit.,[33] 171–174 °C); δ_H(300 MHz; $CDCl_3$) 7.99–7.90 (3 H, m, ArH), 7.80–7.54 (13 H, m, ArH), 7.34–7.28 (2 H, m, ArH), 7.22–7.16 (1 H, m, ArH) and 5.21 ($^2J_{PH}$ 14.5, ArC*H*); *m*/*z* (FAB) 433 (M^+, 99%) and 431 (M^+, 100).

***E*-2,2′-Dibromostilbene.** (2-Bromobenzyl)triphenylphosphonium bromide (85 g, 0.166 mol) was reacted with 2-bromobenzaldehyde (17.6 ml, 0.151 mol) in a method similar to that used in the synthesis of stilbene **2**. The crude product was purified by flash chromatography, eluting with petroleum ether, and recrystallised from petroleum ether to yield the *trans*-stilbene as needles (43.3 g, 78.1%).

In another experiment 2-bromobenzaldehyde (3.16 ml, 27.1 mmol) was reacted according to **method A**. The solid residue was dissolved in dichloromethane and passed through silica. Recrystallisation from petroleum ether yielded the *trans*-stilbene as rectangular plates (3.33 g, 73.2%); mp 109–110 °C (from petroleum ether) (lit.,[34] mp 108.0–108.5 °C); δ_H(300 MHz; $CDCl_3$) 7.69 (2 H, dd, *J* 7.6 and *J* 1.7, 3-ArH), 7.56 (2 H, dd, *J* 7.6 and 1.2, 6-ArH), 7.37 (2 H, s, ArC*H*), 7.30 (2 H, td, *J* 7.6 and 1.2, 4-ArH) and 7.12 (2 H, td, *J* 7.6 and 1.7, 5-ArH); δ_C(75.5 MHz; $CDCl_3$) 136.7 (1-ArC) 133.0, 130.0, 129.2, 127.6, 127.1 and 124.2 (2-ArC).

In another experiment 2-bromobenzaldehyde (3.16 ml, 27.1 mmol) was reacted in a similar way to **method B** used in the synthesis of stilbene **2**. The same work up as previously described yielded the *trans*-stilbene as rectangular plates (2.01 g, 44.1%).

Diols and protection

(1*R*,2*R*)-1,2-Bis(3-fluorophenyl)ethane-1,2-diol. (1*R*,2*R*)-1,2-Bis(3-fluorophenyl)ethane-1,2-diol was prepared by the reported method[8] but was purified by flash chromatography, eluting

with petroleum ether–ethyl acetate, and recrystallised twice from petroleum ether–ethyl acetate (70 : 30) to yield the diol as needles (2.19 g, 95.4%); mp 78–79.5 °C (from petroleum ether–ethyl acetate) (lit.,[8] 79–80 °C); $[\alpha]_D^{22}$ + 103 (*c* 1.00 in $CHCl_3$) (lit.,[8] + 112); δ_F(282.65 MHz, $CDCl_3$) −112.8 (td, $^3J_{HF}$ 7.8 and $^4J_{HF}$ 6.2). The 400 MHz ^{1}H-NMR spectrum of the diol prior to recrystallisation in comparison with a racemic sample, in the presence of Pirkle's reagent, indicated an enantiomeric excess of ≥99%.

(1*RS*,2*RS*)-1,2-Bis(3-fluorophenyl)ethane-1,2-diol. 3,3′-Difluorostilbene **2** (500 mg, 2.31 mmol) was reacted in a method similar to that used in the synthesis of the above diol, except quinuclidine was used instead of $(DHQD)_2PHAL$ and the reaction was stirred at room temperature throughout. The crude product was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallised from petroleum ether–ethyl acetate (90 : 10) to yield the diol as needles (452 mg, 78.1%). Data were identical to the optically pure compound except: mp 118–118.5 °C (from petroleum ether–ethyl acetate) (lit.,[35] 118–119 °C).

(1*R*,2*R*)-1,2-Bis(3,5-difluorophenyl)ethane-1,2-diol. 3,3′,5,5′-Tetrafluorostilbene (814 mg, 3.23 mmol) was reacted in a method similar to that used in the synthesis of (1*R*,2*R*)-1,2-bis(3-fluorophenyl)ethane-1,2-diol. The crude product was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallised from petroleum ether–ethyl acetate (80 : 20) to yield the *diol* as fine needles (861 mg, 93.2%); mp 103–104.5 °C (from petroleum ether–ethyl acetate); $[\alpha]_D^{22}$ +64.5 (*c* 1.00 in CH_2Cl_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 3553 (OH), 3313 br (OH), 1626 (Ar) and 1600 (Ar); δ_H(300 MHz; $CDCl_3$) 6.76–6.63 (6 H, m, ArH), 4.62 (2 H, s, ArC*H*) and 2.68 (2 H, br s, OH); δ_C(75.5 MHz; $CDCl_3$) 162.9 (dd, $^1J_{CF}$ 248.9 and $^3J_{CF}$ 12.4, 3-ArC), 143.4 (t, $^3J_{CF}$ 9.1, 1-ArC), 109.8 (dd, $^2J_{CF}$ 25.4 and $^4J_{CF}$ 8.1, 2-ArC), 103.7 (t, $^2J_{CF}$ 25.4, 4-ArC) and 77.9 (t, $^4J_{CF}$ 1.2, Ar*C*H); *m*/*z* (CI) 270.0656 ([MH]$^+$ − OH. $C_{14}H_{10}F_4O$ requires 270.0668) and 269 ([MH]$^+$ − H_2O, 100%).

(1*R*,2*R*)-1,2-Bis(2-bromophenyl)ethane-1,2-diol. 2,2′-Dibromostilbene (65.0 g, 0.193 mol) was reacted in a method similar to that used in the synthesis of (1*R*,2*R*)-1,2-bis(3-fluorophenyl)ethane-1,2-diol. The crude product was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallised from petroleum ether–ethyl acetate (70 : 30) to yield the diol as needles (68.7 g, 96.0%); mp 107–108.5 °C (from petroleum ether–ethyl acetate) (lit.,[34] 105.5–106.0 °C); $[\alpha]_D^{22}$ −37 (*c* 1.20 in ether) (lit.,[34] +39.9 for (*S*,*S*) enantiomer) and 2,2′-dibromobenzil as a yellow powder (1.49 g, 2.1%); mp 123–125 °C (from petroleum ether–ethyl acetate) (lit.,[36] 115–120 °C); δ_H(300 MHz; $CDCl_3$) 8.03–7.98 (2 H, m, ArH), 7.72–7.68 (2 H, m, ArH), 7.51 (2 H, td, *J* 7.5 and 2.0, 4 or 5-ArH) and 7.47 (2 H, td, *J* 7.5 and 2.0, 4 or 5-ArH); δ_C(75.5 MHz; $CDCl_3$) 191.1 (Ar*C*O), 134.6, 134.4, 134.1, 133.3, 127.6 and 123.2. The 400 MHz ^{1}H-NMR spectrum of the dimethyl ether derivative **8** in comparison with a racemic sample (*rac*-**8**), in the presence of Pirkle's reagent,[37] indicated an enantiomeric excess of ≥99%.

(1*RS*,2*RS*)-1,2-Bis(2-bromophenyl)ethane-1,2-diol. 2,2′-Dibromostilbene (500 mg, 1.49 mmol) was reacted in a method similar to that used in the synthesis of (1*R*,2*R*)-1,2-bis(3-fluorophenyl)ethane-1,2-diol. The crude product was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallised from petroleum ether–ethyl acetate (90 : 10) to yield the diol as needles (404 mg, 73.4%). Characterisation data were identical to the enantiomerically pure compound except; mp 121–122 °C (from petroleum ether–ethyl acetate) (lit.,[34] 118.5–119.0 °C).

(1*R*,2*R*)-1,2-Bis(3-fluorophenyl)-1,2-dimethoxyethane 3. (1*R*,2*R*)-1,2-Bis(3-fluorophenyl)-1,2-dimethoxyethane **3** was prepared in the manner reported[8] but purified by flash chromatography, eluting with petroleum ether–ethyl acetate and recrystallised from petroleum ether–ethyl acetate (90 : 10) to yield the diether as needles (1.97 g, 97.9%); mp 87.5–88 °C (from petroleum ether–ethyl acetate)(lit.,[8] 88–88.5 °C); $[\alpha]_D^{22}$ −48.2 (*c* 1.00 in CH_2Cl_2) (lit.,[8] −50.8) δ_F(282.65 MHz, $CDCl_3$) −113.4 (td, $^3J_{HF}$ 8.4 and $^4J_{HF}$ 5.8).

(1*R*,2*R*)-1,2-Bis(3,5-difluorophenyl)-1,2-dimethoxyethane 11. (1*R*,2*R*)-1,2-Bis(3,5-difluorophenyl)ethane-1,2-diol (190 mg, 0.664 mmol) was reacted in a method similar to that used in the synthesis of diether **3**. The crude product was purified by flash chromatography, eluting with petroleum ether, and recrystallised from petroleum ether to yield the *diether* as a powder (202 mg, 96.8%); mp 54–55.5 °C (from petroleum ether); $[\alpha]_D^{22}$ −58.4 (*c* 1.00 in CH_2Cl_2); $\nu_{max}(CDCl_3)/cm^{-1}$ 2830 (CO), 1600 (Ar) and 1515 (Ar); δ_H(300 MHz; $CDCl_3$) 6.64 (2 H, t, $^3J_{HF}$ 8.8, 4-ArH), 6.63–6.56 (4 H, m, ArH), 4.29 (2 H, s, ArC*H*) and 3.30 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 162.7 (dd, $^1J_{CF}$ 248.9 and $^3J_{CF}$ 12.4, 3-ArC), 142.0 (t, $^3J_{CF}$ 8.0, 1-ArC), 110.4 (dd, $^2J_{CF}$ 17.4 and $^4J_{CF}$ 8.1, 2-ArC), 103.3 (t, $^2J_{CF}$ 25.4, 4-ArC), 85.7 (t, $^4J_{CF}$ 1.8, Ar*C*H) and 57.5 (OMe); *m*/*z* (CI) 283.0746 ([MH]$^+$ − MeOH. $C_{15}H_{11}F_4O$ requires 283.0746) and 157 (100%).

(1*R*,2*R*)-1,2-Bis(2-bromophenyl)-1,2-dimethoxyethane 8. (1*R*,2*R*)-1,2-Bis(2-bromophenyl)ethane-1,2-diol (25.0 g, 67.6 mmol) was reacted in a method similar to that used in the synthesis of diether **3**. The crude product was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallised from petroleum ether–ethyl acetate (95 : 5) to yield the diether as rectangular prisms (26.7 g, 99.2%); mp 90–91 °C (from petroleum ether) (lit.,[8] 85–85.5 °C); $[\alpha]_D^{22}$ −107 (*c* 1.10 in CH_2Cl_2) (lit.,[8] −109).

(1*RS*,2*RS*)-1,2-Bis(2-bromophenyl)-1,2-dimethoxyethane rac-8. (1*RS*,2*RS*)-1,2-Bis(2-bromophenyl)ethane-1,2-diol (300 mg, 0.81 mmol) was reacted in a method similar to that used in the synthesis of diether **3**. The crude product was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallised from petroleum ether–ethyl acetate (90 : 10) to yield the diether as rectangular prisms (318 mg, 98.6%). Characterisation data were identical to the enantiomerically pure compound except; mp 121–122 °C (from petroleum ether–ethyl acetate) (lit.,[8] 115.5–116 °C).

(1*R*,2*R*)-1,2-Bis(3-fluorophenyl)-1,2-bis(methoxymethoxy)-ethane 10. Chloromethyl methyl ether (0.91 ml, 12.0 mmol) was added dropwise to a solution of (1*R*,2*R*)-1,2-bis(3-fluorophenyl)-ethane-1,2-diol (1.50 g, 6.00 mmol) in dry dichloromethane (30 ml) under an argon atmosphere. Hunig's base (1.57 ml, 9.00 mmol) was added to the solution and the reaction stirred for 72 h. The reaction was quenched with 1 M hydrochloric acid (30 ml). The layers were separated, the aqueous layer extracted with dichloromethane

(3 × 15 ml) and the combined organic extracts washed with a saturated sodium chloride solution (30 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, to yield the *acetal* as an oil (1.71 g, 84.2%); $[a]_D^{22}$ −130 (*c* 1.00 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 1614 (Ar), 1592 (Ar), 1488 (Ar) and 1103 (CO); δ_H(300 MHz; $CDCl_3$) 7.20 (2 H, td, *J* 8.4 and $^4J_{HF}$ 5.7, 5-ArH), 7.04–6.98 (4 H, m, 2 and 6-ArH), 6.93 (2 H, tdd, $^3J_{HF}$ 8.4, *J* 8.4, 2.6 and 1.1, 4-ArH), 4.82 (2 H, s, Ar*C*H), 4.58 (2 H, d, *J* 6.8, OCH_AH$_B$O), 4.54 (2 H, d, *J* 6.8, OCH$_A$$H_B$O) and 3.09 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 162.6 ($^1J_{CF}$ 245.1, 3-ArH), 141.1 ($^3J_{CF}$ 6.9, 1-ArC), 129.4 ($^3J_{CF}$ 8.0, 5-ArC), 123.2 ($^4J_{CF}$ 2.5, 6-ArC), 114.6 ($^2J_{CF}$ 21.1, 2-ArC), 114.4 ($^2J_{CF}$ 22.3, 4-ArC), 94.6 (OCH_2O), 80.1 ($^4J_{CF}$ 1.9, Ar*C*H) and 55.3 (OMe); δ_F(282.65 MHz, $CDCl_3$) −113.2 (td, $^3J_{HF}$ 8.4 and $^4J_{HF}$ 5.7); *m*/*z* (CI) 339.1393 ([MH]$^+$. $C_{18}H_{21}F_2O_4$ requires 339.1408), 323 ([MH]$^+$ − Me, 2%) and 245 ([MH]$^+$ − Ar, 100).

(1*R*,2*R*)-1,2-Bis(2-bromophenyl)-1,2-bis(methoxymethoxy)-ethane 9. (1*R*,2*R*)-1,2-Bis(2-bromophenyl)ethane-1,2-diol (1.21 g, 3.27 mmol) was reacted in a method similar to that used in the synthesis of *acetal* **10**. The crude product was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallised from petroleum ether–ethyl acetate (90 : 10) to yield the *acetal* as a powder (1.22 g, 81.6%); mp 76–77 °C (from petroleum ether–ethyl acetate); $[a]_D^{22}$ −134.2 (*c* 1.00 in CH_2Cl_2); ν_{max}(CH_2Cl_2)/cm^{-1} 2844 (CO), 2825 (CO) 1592 (Ar) and 1568 (Ar); δ_H(300 MHz; $CDCl_3$) 7.72 (2 H, dd, *J* 7.7 and 1.7, 3-ArH), 7.50 (2 H, dd, *J* 7.7 and 1.2, 6-ArH), 7.33 (2 H, td, *J* 7.7 and 1.2, 4-ArH), 7.12 (2 H, td, *J* 7.7 and 1.7, 5-ArH), 5.40 (2 H, s, Ar*C*H), 4.40 (4 H, s, OCH_2O) and 2.87 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 137.9 (2-ArC) 132.6 (6-ArC), 131.0 (3-ArC), 129.2 (5-ArC), 127.0 (4-ArC), 123.2 (1-ArC), 95.0 (OCH_2O), 76.7 (Ar*C*H) and 55.4 (OMe); *m*/*z* (CI) 458.9805 ([MH]$^+$. $C_{18}H_{20}Br_2O_4$ requires 458.9807), 397 ([MH]$^+$ − $MeOCH_2OH$, 40%) and 367 (100).

(4*R*,5*R*)-2,2-Dimethyl-4,5-bis(3-fluorophenyl)-1,3-dioxolane 4. (1*R*,2*R*)-1,2-Bis(3-fluorophenyl)ethane-1,2-diol (1.05 g, 4.20 mmol), was dissolved in anhydrous toluene (30 ml) under an argon atmosphere. Then 2,2-dimethoxypropane (2.50 ml, 20.4 mmol) and *p*-toluenesulfonic acid (30.0 mg, 0.174 mmol) were added to the solution. The reaction was heated to 40 °C and stirred at that temperature for 2 h. 1.25 M sodium hydroxide (4.2 ml) was added, the solution allowed to cool to room temperature and stirred overnight. The mixture was extracted with dichloromethane (3 × 20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallised from petroleum ether–ethyl acetate (95 : 5) to yield the *dioxolane* as rectangular plates (1.17 g, 95.2%); mp 146–147 °C (from petroleum ether–ethyl acetate); $[a]_D^{22}$ +40 (*c* 1.00 in $CHCl_3$); ν_{max}(CH_2Cl_2)/cm^{-1} 1615 (Ar) 1594 (Ar), 1453 (Ar), 1374 (CMe_2) and 1142 (CO); δ_H(300 MHz; $CDCl_3$) 7.33–7.24 (2 H, m, 5-ArH); 7.06–6.98 (4 H, m, 4 and 6-ArH), 6.92 (2 H, dt, $^3J_{HF}$ 8.4 and *J* 1.3, 2-ArH), 4.69 (2 H, s, Ar*C*H) and 1.67 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 162.9 ($^1J_{CF}$ 245.7, 3-ArH), 139.2 ($^3J_{CF}$ 7.4, 1-ArC), 130.0 ($^3J_{CF}$ 8.7, 5-ArC), 122.4 ($^4J_{CF}$ 3.1, 6-ArC), 115.4 ($^2J_{CF}$ 21.1, 2 or 4-ArC), 113.4 ($^2J_{CF}$ 22.3, 2 or 4-ArC), 109.9 (OCO), 84.7 ($^4J_{CF}$ 1.8, Ar*C*H) and 27.1 (Me); δ_F(282.65 MHz, $CDCl_3$) −112.4 (td, $^3J_{HF}$ 8.4 and $^4J_{HF}$ 5.5), *m*/*z* (CI) 275.0877 ([MH]$^+$ − Me. $C_{16}H_{13}F_2O_2$ requires 275.0844), 233 ([MH]$^+$ − $(Me)_2CO$, 4%) and 57 (100).

(4*R*,5*R*)-2,2-Dimethyl-4,5-bis(2-bromophenyl)-1,3-dioxolane 6. (1*R*,2*R*)-1,2-Bis(2-bromophenyl)ethane-1,2-diol (5.00 g, 13.5 mmol) was reacted in a method similar to that used in the synthesis of dioxolane **4**. The crude product was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallised from petroleum ether–ethyl acetate (95 : 5) to yield the dioxolane as rectangular prisms (5.37 g, 96.4%); mp 112–113 °C (from petroleum ether) (lit.,[8] 114–115 °C); $[a]_D^{22}$ −11.7 (*c* 0.920 in $CHCl_3$) (lit.,[8] −11.4).

(1*R*,2*R*)-1,2-Bis(3-fluorophenyl)-1,2-bis[(1,1-dimethylethyl)dimethylsiloxy]ethane 5. (1*R*,2*R*)-1,2-Bis(3-fluorophenyl)ethane-1,2-diol (200 mg, 0.80 mmol) was dissolved in dry dichloromethane (10 ml) under an argon atmosphere. *tert*-Butyldimethylsilyl triflate (0.37 ml, 1.60 mmol) was added to the solution, followed by 2,6-lutidene (0.279 ml, 2.40 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with saturated ammonium chloride solution (2 ml), the layers separated and the aqueous layer extracted with dichloromethane (3 × 5 ml). The combined organic extracts were washed with a saturated sodium chloride solution (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with petroleum ether-ethyl acetate, and recrystallised twice from petroleum ether–ethyl acetate (95 : 5) to yield the *silyl ether* as rectangular plates (284 mg, 97.8%); mp 87–87.5 °C (from petroleum ether); $[a]_D^{22}$ −48 (*c* 1.00 in CH_2Cl_2); ν_{max}(CH_2Cl_2)/cm^{-1} 1588 (Ar), 1482 (Ar), 1366 (CMe_3) and 1260 (SiMe); δ_H(300 MHz; $CDCl_3$) 7.12 (2 H, td, *J* 8.5 and $^4J_{HF}$ 5.6, 5-ArH), 7.98–6.75 (6 H, m, ArH), 4.71 (2 H, s, Ar*C*H), 0.88 (9H, s, $C(Me)_3$), −0.08 (3 H, s, SiMe_AMe$_B$) and −0.20 (3 H, s, SiMe$_A$$Me_B$); δ_C(75.5 MHz; $CDCl_3$) 162.2 ($^1J_{CF}$ 243.9, 3-ArH), 143.7 ($^3J_{CF}$ 7.5, 1-ArC), 128.5 ($^3J_{CF}$ 8.4, 5-ArC), 122.9 ($^4J_{CF}$ 2.5, 6-ArC), 114.3 ($^2J_{CF}$ 21.7, 2 or 4-ArC), 113.9 ($^2J_{CF}$ 21.1, 2 or 4-ArC), 78.4 ($^4J_{CF}$ 1.8, Ar*C*H), 25.8 ($C(CH_3)_3$), 18.1 ($C(Me)_3$), −5.0 (SiMe_AMe$_B$) and −5.2 (SiMe$_A$$Me_B$); δ_F(282.65 MHz, $CDCl_3$) −114.6 (td, $^3J_{HF}$ 8.5 and $^4J_{HF}$ 5.6); *m*/*z* (CI) 459 ([MH]$^+$ − HF, 10%), 421.1840 ([MH]$^+$ − $(Me)_2CH$. $C_{23}H_{33}F_2O_2Si_2$ requires 421.1831), 347 ([MH]$^+$ − TBSOH, 26%), 217 ([MH]$^+$ − 2 × TBSOH, 28) and 85 (CH_2Cl_2, 100).

(1*R*,2*R*)-1,2-Bis(2-bromophenyl)-1,2-bis[(1,1-dimethylethyl)-dimethylsiloxy]ethane 7. (1*R*,2*R*)-1,2-Bis(2-bromophenyl)-ethane-1,2-diol (5.00 g, 13.5 mmol) was reacted in a method similar to that used in the synthesis of silyl ether **5**. The crude product was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallised from petroleum ether–ethyl acetate (90 : 10) to yield the silyl ether as rectangular prisms (7.71 g, 96.1%); mp 145–147 °C (from petroleum ether) (lit.,[8] 140–141 °C); $[a]_D^{22}$ −40.7 (*c* 1.00 in CH_2Cl_2) (lit.[8] −39.5).

Lithiation experiments

Lithiation and methylation of (1*R*,2*R*)-1,2-bis(3-fluorophenyl)-1,2-dimethoxyethane 3. Diether **3** (28.0 mg, 0.10 mmol) was dissolved in dry THF (1 ml) under an argon atmosphere and cooled to −78 °C. Then 1.25 M *sec*-BuLi (0.19 ml, 0.25 mmol) was added dropwise to the stirred solution. After the addition was complete the reaction was stirred for 3 h at this temperature.

Methyl iodide (0.025 ml, 0.4 mmol.) was added, the reaction stirred for a further 1 h at −78 °C before the solution was allowed to slowly warm to room temperature and stirred overnight. 2 M potassium hydroxide (2 ml) was added, the solution stirred for 4 h and then diluted with diethyl ether (5 ml). The layers were separated and the aqueous layer extracted with diethyl ether (3 × 5 ml). The combined organic extracts were washed with a saturated sodium chloride solution (25 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The solid residue was dissolved in dichloromethane (5 ml), passed through a pad of silica and concentrated under reduced pressure to yield a yellow oil. ^{1}H-NMR spectroscopy indicated the formation of dimethylated species (96%); δ_H(300 MHz; $CDCl_3$) 7.19 (2 H, dd, *J* 7.9 and 1.3, 6-ArH), 7.10 (2 H, td, *J* 7.9 and $^4J_{HF}$ 5.5, 5-ArH), 6.88 (2 H, ddd, $^3J_{HF}$ 9.6, *J* 7.9 and 1.3, 4-ArH), 4.66 (2 H, s, ArC*H*), 3.28 (6 H, s, OMe) and 1.76 (6 H, d, $^4J_{HF}$ 2.2, ArCH_3); δ_F(282.65 MHz, $CDCl_3$) −115.9 (m), and starting material (4%).

Lithiation and methylation of (4*R*,5*R*)-2,2-dimethyl-4,5-bis(3-fluorophenyl)-1,3-dioxolane 4. Dioxolane **4** (35 mg, 0.121 mmol) was reacted in a method similar to diether **3**. ^{1}H-NMR spectroscopy indicated the formation of monomethylated species (63%); δ_H(300 MHz; $CDCl_3$) 4.68 (d, *J* 8.4, ArCH_ACH_BAr) and 4.65 (d, *J* 8.4, ArCH$_A$CH_BAr); δ_F (282.65 MHz, $CDCl_3$) −112.5 (1F, td, $^3J_{HF}$ 9.0 and $^4J_{HF}$ 5.5) and −116.8 (1F, dd, $^3J_{HF}$ 9.0 and $^4J_{HF}$ 5.5), dimethylated product (31%), δ_H(300 MHz; $CDCl_3$) 4.64 (s, ArC*H*); δ_F (282.65 MHz, $CDCl_3$) −116.9 (td, $^3J_{HF}$ 9.0 and $^4J_{HF}$ 5.9), and starting material (6%). A similar experiment, using *tert*-BuLi instead of *sec*-BuLi, gave an identical distribution of products.

Lithiation and methylation of (1*R*,2*R*)-1,2-Bis(3-fluorophenyl)-1,2-bis[(1,1-dimethylethyl)dimethylsiloxy]ethane 5. Silyl ether **5** (30 mg, 0.0627 mmol) was reacted in a method similar to that used in the reaction of diether **3**. ^{1}H-NMR spectroscopy indicated the formation of monomethylated species (65%), δ_H(300 MHz; $CDCl_3$) 4.72 (d, *J* 4.5, ArCH_ACH$_B$Ar) and 4.70 (d, *J* 4.5, ArCH$_A$CH_BAr); δ_F (282.65 MHz, $CDCl_3$) −114.8 (1F, td, $^3J_{HF}$ 9.0 and $^4J_{HF}$ 5.5) and −119.2 (1F, dd, $^3J_{HF}$ 9.0 and $^4J_{HF}$ 5.5), dimethylated product (25%); δ_H(300 MHz; $CDCl_3$) 4.64 (s, ArC*H*); δ_F(282.65 MHz, $CDCl_3$) −119.4 (dd, $^3J_{HF}$ 9.0 and $^4J_{HF}$ 5.4) and starting material (10%).

(1*R*,2*R*)-1,2-Bis(3,5-difluoro-4-methylphenyl)-1,2-dimethoxyethane. Diether **11** (100 mg, 0.318 mmol) was reacted in a method similar to that used in the lithiation and methylation of diether **3**, except that the crude product was purified by flash chromatography, eluting with petroleum ether, to yield the *diether* as a yellow oil (92.1 mg, 84.6%); $[\alpha]_D^{22}$ −24.8 (*c* 1.00 in CH_2Cl_2); ν_{max}($CDCl_3$)/cm^{-1} 2828 (CO), 1585 (Ar), 1559 (Ar) and 1500 (Ar); δ_H(270 MHz; $CDCl_3$) 6.56 (4 H, d, $^3J_{HF}$ 7.6, 2-ArH), 4.13 (2 H, s, ArC*H*), 3.18 (6 H, s, OMe) and 2.06 (6 H, t, $^4J_{HF}$ 1.7, ArCH_3); δ_C(67.9 MHz; $CDCl_3$) 161.3 (dd, $^1J_{CF}$ 246.5 and $^3J_{CF}$ 9.3, 3-ArC), 138.0 (t, $^3J_{CF}$ 9.1, 1-ArC), 110.0 (dd, $^2J_{CF}$ 17.1 and $^4J_{CF}$ 9.3, 2-ArC), 86.0 (Ar*C*H), 57.5 (OMe) and 7.0 (t, $^3J_{CF}$ 3.6, ArCH_3); *m*/*z* (CI) 341.1164 ([MH]$^+$. $C_{18}H_{17}O_2F_4$ requires 341.1165), 323 ([MH]$^+$ − HF, 26%), 311 ([MH]$^+$ − MeOH, 57), and 171 (100).

1,2-Bis(2-bromophenyl)ethane 25. 2-Bromobenzyl bromide (36.0 g, 0.144 mmol) was dissolved in dry THF (200 ml) under an argon atmosphere and cooled to −78 °C. Then *n*-BuLi (45 ml of a 1.6 M solution, 0.072 mmol) was added dropwise to the stirred solution. After stirring at this temperature for a further 1 h, water (100 ml) was added and the reaction was allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with diethyl ether (3 × 50 ml). The combined organic extracts were washed with a saturated solution of ammonium chloride (50 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography, eluting with petroleum ether, and recrystallised from petroleum ether to yield the citenzyl as platelets (22.3 g, 91.1%); mp 81–83 °C (from petroleum ether) (lit.,[34] 83–84 °C); δ_H(300 MHz; $CDCl_3$) 7.55 (2 H, dd, *J* 7.9 and 1.6, 3-ArH), 7.26–7.16 (4 H, m, ArH), 7.10–7.04 (2 H, m, ArH) and 3.04 (4 H, s, ArCH_2); δ_C(75.5 MHz; $CDCl_3$) 140.6 (1-ArC) 132.8 (ArC), 130.6 (ArC), 127.8 (ArC), 127.4 (ArC), 124.5 (2-ArC) and 36.4 (Ar*C*H$_2$).

General methods

Sulfur diimidazole. Sulfur dichloride (1.72 ml, 27.1 mmol) was added to dry hexane (30 ml) under an argon atmosphere. The reaction mixture was cooled to 0 °C before the dropwise addition of 1-(trimethylsilyl)imidazole (6.32 ml, 43.2 mmol). A white precipitate formed immediately. The suspension was slowly allowed to warm to room temperature and stirred at this temperature for 0.5 h. The suspension was filtered under an argon atmosphere and washed through with more dry hexane (20 ml). The residual solvent was removed by passing a strong flow of argon through the precipitate for 0.1 h. Then dry THF (30 ml) was added to the precipitate under an argon atmosphere. The fine suspension was immediately added to the prepared lithiated compound. The yield of sulfur diimidazole was assumed to be quantitative.

Sulfur dibenzotriazole 19. Sulfur dichloride (0.18 ml, 2.26 mmol) was reacted with *N*-trimethylsilyl-1*H*-benzotriazole (0.95 ml, 5.24 mmol) in a method similar to the preparation of disulfur diimidazole. The yield of sulfur dibenzotriazole was assumed to be quantitative.

Method C. General procedure for the preparation of the sulfides by *ortho*-lithiation. The thiepine precursor (1.80 mmol) was dissolved in dry THF (5 ml) under an argon atmosphere and cooled to −78 °C. Then *sec*-BuLi (3.60 ml of a 1.25 M solution, 4.5 mmol) was added dropwise to the stirred solution. After the addition was complete the solution was stirred for a further 3 h at −78 °C. The electrophile (10.8 mmol) was then added and the reaction was stirred for a further 1 h at this temperature before being allowed to warm to room temperature overnight. Water was added and the reaction stirred for 0.5 h. The layers were separated and the aqueous layer extracted with dichloromethane (3 × 10 ml). The combined organic extracts were washed with a saturated solution of ammonium chloride (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was subsequently purified.

Method D. General procedure for the preparation of the sulfides by bromine–lithium exchange. The thiepine precursor (1.25 mmol) was dissolved in dry THF (1 ml) under an argon atmosphere and cooled to −78 °C. Then *tert*-BuLi (2.94 ml of a 1.70 M solution, 5.0 mmol) was added dropwise to the stirred solution. After the addition was complete the solution was stirred for a further 0.5 h at −78 °C, allowed to slowly warm to −10 °C and stirred for 0.5 h at this temperature. The solution was recooled

to −78 °C and stirred at this temperature for 0.5 h. The electrophile (7.50 mmol) was then added and the reaction stirred for a further 1 h at this temperature before being allowed to warm to room temperature overnight. Water was added and the reaction stirred for 0.5 h. The layers were separated and the aqueous layer extracted with dichloromethane (3 × 5 ml). The combined organic extracts were washed with a saturated solution of ammonium chloride (5 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was subsequently purified.

Method E. General procedure for the preparation of the unsubstituted sulfides. 2-Bromobibenzyl **25** (2.10 g, 6.18 mmol) was dissolved in dry THF (20 ml) under an argon atmosphere and cooled to −78 °C. Then *n*-BuLi (5.44 ml of a 2.5 M solution, 13.6 mmol) was added dropwise to the stirred solution. After the addition was complete the reaction solution is stirred for a further 0.5 h at −78 °C. The electrophile (37.1 mmol) was then added and the reaction was stirred for a further 1 h at this temperature before being allowed to warm to room temperature overnight. Water (10 ml) was added and the reaction stirred for 0.5 h. The layers were separated and the aqueous layer extracted with dichloromethane (3 × 10 ml). The combined organic extracts were washed with a saturated solution of ammonium chloride (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was subsequently purified.

Thiepine syntheses

(10*R*,11*R*)-4,6-Difluoro-10,11-dimethoxy-10,11-dihydrodibenzo-[*b*,*f*]thiepine 14. Diether **3** (500 mg, 1.80 mmol) was reacted according to **method C** using sulfur diimidazole (1.79 g, 10.8 mmol) as the electrophile. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallisation twice from petroleum ether yielded the *sulfide* as a powder (265 mg, 47.8%); mp 145–145.5 °C (from petroleum ether); $[\alpha]_D^{22}$ +108 (*c* 1.00 in CH_2Cl_2); (Found: C, 62.27; H, 4.46; F, 12.66; S, 10.41. $C_{16}H_{14}F_2O_2S$ requires C, 62.30; H, 4.50; F, 12.66; S, 10.49%); $\nu_{max}(CH_2Cl_2)$/cm $^{-1}$ 2853 (OC–H_3), 1573 (Ar) and 1122 (CO); δ_H(300 MHz; $CDCl_3$) 7.32–7.19 (4 H, m, 1 and 2-ArH), 6.98 (2 H, td, $^3J_{HF}$ 8.4, *J* 8.4 and 1.8, 3-ArH), 5.09 (2 H, s, ArC*H*) and 3.48 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 161.1 ($^1J_{CF}$ 246.4, 4-ArH), 142.5 (11a-ArC), 129.6 ($^3J_{CF}$ 8.1, 2-ArC), 125.6 ($^4J_{CF}$ 3.1, 1-ArC), 123.0 ($^2J_{CF}$ 19.2, 4a-ArC), 114.7 ($^2J_{CF}$ 23.6, 3-ArC), 83.1 ($^4J_{CF}$ 3.1, Ar*C*H) and 57.1 (OMe); δ_F(282.65 MHz, $CDCl_3$) −107.9 (dd, $^3J_{HF}$ 8.4 and $^4J_{HF}$ 5.0); *m*/*z* (EI) 308 (M^+, 2%) 276 (M^+ − MeOH, 98), 244 (M^+ − 2 × MeOH, 40) and 233 (100).

In another experiment diether **3** (500 mg, 1.80 mmol) was reacted according to **method C** using sulfur dichloride (0.69 ml, 10.8 mmol) as the electrophile. The same purification yielded the *sulfide* as a powder (16.6 mg, 3.0%).

(10*R*,11*R*)-4,6-Difluoro-10,11-di(methoxymethoxy)-10,11-dihydrodibenzo[*b*,*f*]thiepine 20. Diether **10** (159 mg, 0.470 mmol) was reacted according to **method C** using sulfur diimidazole (430 mg, 2.59 mmol) as the electrophile. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate yielded the *sulfide* as a powder (64.2 mg, 37.1%); mp 122–122.5 °C (from petroleum ether–ethyl acetate); $[\alpha]_D^{22}$ +25.5 (*c* 1.00 in CH_2Cl_2); $\nu_{max}(CH_2Cl_2)$/cm $^{-1}$ 2825 (CO), 1610 (Ar), 1576 (Ar) and 705 (C–S); δ_H(300 MHz; $CDCl_3$) 7.29–7.21 (4 H, m, 1 and 2-ArH), 7.01–6.93 (2 H, m, 3-ArH), 5.46 (2 H, s, Ar*C*H), 4.95 (2 H, d, *J* 6.8, OCH_ACH_BO), 4.73 (2 H, d, *J* 6.8, OCH$_A$CH_BO) and 3.42 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 161.1 ($^1J_{CF}$ 246.3, 4-ArH), 142.3 ($^3J_{CF}$ 8.0, 11a-ArC), 129.5 ($^3J_{CF}$ 8.1, 2-ArC), 126.2 ($^4J_{CF}$ 3.7, 1-ArC), 123.2 ($^2J_{CF}$ 19.2, 4a-ArC), 114.7 ($^2J_{CF}$ 23.5, 3-ArC), 96.1 (OCH_2O), 79.6 ($^4J_{CF}$ 3.1, Ar*C*H) and 56.1 (OMe); δ_F(282.65 MHz, $CDCl_3$) −107.8 (dd, $^3J_{HF}$ 6.5 and $^4J_{HF}$ 3.7); *m*/*z* (EI) 368.0900 (M^+. $C_{18}H_{18}O_4F_2S$ requires 368.0894), 307 (M^+ − CH_3OCH_2OH, 48%), 244 (M^+ − 2 × CH_3OCH_2OH, 28), and 233 (ArSArCH, 100).

(10*R*,11*R*)-4,6-Difluoro-10,11-dimethoxy-10,11-dihydrodibenzo-[*b*,*f*]thiepine 5-oxide 27. Diether **3** (100 mg, 0.360 mmol) was reacted according to **method C** using thionyl chloride (1.86 µl, 1.85 mmol) as the electrophile. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallisation from petroleum ether gave the *sulfoxide* as a powder (9.8 mg, 8.4%); mp 87–89.5 °C (from petroleum ether); $[\alpha]_D^{22}$ −15 (*c* 1.00 in CH_2Cl_2); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 1597 (Ar), 1574 (Ar) and 1042 (SO); δ_H(300 MHz; $CDCl_3$) 7.60 (1 H, br d, *J* 8.2, 1 or 9-ArH), 7.49 (1 H, td, *J* 8.2 and $^4J_{HF}$ 5.5, 2 or 8-ArH), 7.46 (1 H, td, *J* 8.2 and $^4J_{HF}$ 5.5, 2 or 8-ArH), 7.34 (1 H, br d, *J* 8.2, 1 or 9-ArH), 7.10 (1 H, td, $^3J_{HF}$ 8.2, *J* 8.2 and 1.3, 3 or 7-ArH), 7.00 (1 H, br t, $^3J_{HF}$ 8.2 and *J* 8.2, 3 or 7-ArH), 6.75 (1 H, d, *J* 8.2, ArCH_ACH_BAr), 4.65 (1 H, d, *J* 9.0, ArCH$_A$CH_BAr), 3.63 (3 H, s, OMe_A) and 3.38 (3 H, s, OMe_B); δ_C(75.5 MHz; $CDCl_3$) 159.3 ($^1J_{CF}$ 252.0, 4 or 6-ArH), 158.2 ($^1J_{CF}$ 246.4, 4 or 6-ArH), 141.5 ($^3J_{CF}$ 8.1, 9a or 11a-ArC), 139.0 ($^3J_{CF}$ 8.1, 9a or 11a-ArC), 134.2 ($^3J_{CF}$ 9.3, 2 or 8-ArC), 133.6 ($^3J_{CF}$ 8.8, 2 or 8-ArC), 130.3 ($^4J_{CF}$ 3.2, 1 or 9-ArC), 122.2 ($^4J_{CF}$ 3.1, 1 or 9-ArC), 116.2 ($^2J_{CF}$ 23.6, 3 or 7-ArC), 115.4 ($^2J_{CF}$ 21.7, 3 or 7-ArC), 83.8 ($^4J_{CF}$ 3.2, ArC_AH), 75.6 ($^4J_{CF}$ 3.2, ArC_BH), 58.8 (OC_AH$_3$) and 54.5 (C_BH$_3$); δ_F(282.65 MHz, $CDCl_3$) −110.9 (1F, dd, $^3J_{HF}$ 9.0 and $^4J_{HF}$ 5.5) and −113.2 (1F, dd, $^3J_{HF}$ 8.2 and $^4J_{HF}$ 5.4); *m*/*z* (CI) 325 ([M(C_2H_5)]$^+$, 10%), 325.0703 ([MH]$^+$. $C_{16}H_{15}F_2O_2S$ requires 325.0710), 293 ([MH]$^+$ − MeOH, 84) and 277 ([MH]$^+$ − SO, 12).

(10*R*,11*R*)-4,6-Difluoro-10,11-dimethoxy-10,11-dihydrodibenzo-[*b*,*f*]thiepine 5-dioxide 12. Diether **3** (100 mg, 0.36 mmol) was reacted according to **method C** using sulfuryl dichloride (0.17 ml, 2.16 mmol) as the electrophile. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallisation from petroleum ether yielded the *sulfone* as a fine powder (23.0 mg, 18.8%); mp 87–89 °C (from petroleum ether); $[\alpha]_D^{22}$ +72 (*c* 1.00 in CH_2Cl_2); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 2828 (CO), 1597 (Ar) and 1574 (Ar); δ_H(300 MHz; $CDCl_3$) 7.48 (2 H, td, *J* 8.1 and $^4J_{HF}$ 5.4, 2-ArH), 7.27–7.25 (2 H, m, 3-ArH), 6.81 (2 H, dt, *J* 8.1 and 1.2, 1-ArH), 5.98 (2 H, s, ArC*H*) and 3.29 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 159.6 ($^1J_{CF}$ 260.7, 4-ArC), 138.7 ($^3J_{CF}$ 8.1, 11a-ArC), 135.0 ($^3J_{CF}$ 10.6, 2-ArC), 134.0 ($^2J_{CF}$ 19.2, 4a-ArC), 124.0 ($^4J_{CF}$ 3.7, 1-ArC), 117.4 ($^2J_{CF}$ 22.9, 3-ArC), 76.7 ($^4J_{CF}$ 2.5, Ar*C*H) and 57.9 (OMe); δ_F(282.65 MHz, $CDCl_3$) −102.1 (dd, $^3J_{HF}$ 8.1 and $^4J_{HF}$ 5.4); *m*/*z* (CI) 341.0652 ([MH]$^+$. $C_{16}H_{15}O_4F_2S$ requires 341.0659), 309 ([MH]$^+$ − MeOH, 10%), 277 ([MH]$^+$ − 2MeOH, 59) and 65 (100), *(1R,2R)-1,2-bis(2-chloro-3-fluorophenyl)-1,2-dimethoxyethane* **13** as a yellow powder (48.7 mg, 39.0%); mp 67–71 °C (from petroleum ether–ethyl acetate); $[\alpha]_D^{22}$ −76.9 (*c* 1.00 in CH_2Cl_2); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 2829 (CO), 1594 (Ar) and 1576 (Ar); δ_H(300 MHz; $CDCl_3$) 7.43 (2 H, dt, *J* 8.1 and 1.5, 6-ArH), 7.26 (2 H, td, *J* 8.1 and $^4J_{HF}$ 5.3, 5-ArH), 7.05 (2 H, td, $^3J_{HF}$ 8.1, *J* 8.1 and 1.5, 4-ArH), 4.93 (2 H, s,

ArC*H*) and 3.18 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 157.7 ($^1J_{CF}$ 247.6, 3-ArC), 138.0 ($^3J_{CF}$ 6.9, 1-ArC), 127.3 ($^3J_{CF}$ 8.1, 5-ArC), 124.9 ($^4J_{CF}$ 2.5, 6-ArC), 121.2 ($^4J_{CF}$ 21.0, 2-ArC), 115.7 ($^2J_{CF}$ 21.1, 4-ArC), 81.0 ($^4J_{CF}$ 2.5, Ar*C*H) and 57.7 (OMe); δ_F(282.65 MHz, $CDCl_3$) −114.0 (dd, $^3J_{HF}$ 8.1 and $^4J_{HF}$ 5.4); *m*/*z* (CI) 347.0420 ($[MH]^+$. $C_{16}H_{14}Cl_2F_2O_2$ requires 347.0417), 315 ($[MH]^+$ − MeOH, 25%) and 85 (CH_2Cl_2, 100), and *(1R,2R)-1-(2-chloro-3-fluoro)-2-(3-fluorophenyl)-1,2-dimethoxyethane* as a yellow oil (7.7 mg, 6.9%); $[\alpha]_D^{22}$ −93.7 (*c* 1.00 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2828 (CO), 1599 (Ar) and 1576 (Ar); δ_H(300 MHz; $CDCl_3$) 7.72–7.60 (2 H, m, ArH), 7.30–7.20 (3 H, m, ArH), 7.09–7.02 (2 H, m, ArH), 5.84 (1 H, d, *J* 6.0, ArCH_A), 5.03 (1 H, d, *J* 6.0, ArCH_B), 3.29 (3 H, s, OMe_A) and 3.17 (3 H, s, OMe_B); δ_C(75.5 MHz; $CDCl_3$) 159.5 ($^1J_{CF}$ 262.3, 3 or 3′-ArC), 157.9 ($^1J_{CF}$ 255.3, 3 or 3′-ArC), 140.1 (1-ArC), 137.5 (1-ArC), 135.8 ($^3J_{CF}$ 9.9, 5 or 5′-ArC), 127.4 ($^3J_{CF}$ 7.8, 5 or 5′-ArC), 126.3 ($^4J_{CF}$ 3.2, 6 or 6′-ArC), 125.2 ($^4J_{CF}$ 3.6, 6 or 6′-ArC), 121.4 ($^2J_{CF}$ 17.7, 2-ArC), 117.6 ($^2J_{CF}$ 22.8, ArC), 115.9 ($^2J_{CF}$ 21.3, ArC), 80.8 (ArC_AH), 78.8 (ArC_BH), 58.1 (OMe_A) and 57.4 (OMe_B); δ_F(282.65 MHz, $CDCl_3$) −102.0 (1F, dd, $^3J_{HF}$ 10.4 and $^4J_{HF}$ 5.1) and −113.5 (1F, m); *m*/*z* (CI) 281.0522 ($[MH]^+$ − MeOH. $C_{15}H_{11}ClF_2O$ requires 281.0545), 173 (FClArCHOMe, 32%) and 139 (ArCHOMe, 84).

(10*R*,11*R*)-10,11-Dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepine 15. Diether **8** (500 mg, 1.25 mmol) was reacted according to **method D** using sulfur diimidazole (2.58 g, 7.50 mmol) as the electrophile. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallisation from methanol and (α,α′,α″)-trifluorotoluene, yielded the *sulfide* as fine needles (130 mg, 38.2%); mp 63–64.5 °C (from methanol); $[\alpha]_D^{22}$ −33.2 (*c* 1.00 in CH_2Cl_2); ν_{max}(CH_2Cl_2)/cm^{-1} 2821 (CO), 1588 (Ar), 1573 (Ar) and 700 (C–S); δ_H(300 MHz; $CDCl_3$) 7.53 (2 H, dd, *J* 7.6 and 1.0, 1 or 4-ArH), 7.44 (2 H, dd, *J* 7.6 and 1.6, 1 or 4-ArH), 7.28 (2 H, td, *J* 7.6 and 1.3, 2 or 3-ArH), 7.13 (2 H, td, *J* 7.6 and 1.6, 2 or 3-ArH), 5.11 (2 H, s, ArC*H*) and 3.46 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 139.4 (4a or 11a-ArC), 136.5 (4a or 11a-ArC), 132.3 (1 or 4-ArC), 130.2 (1 or 4-ArC), 128.2 (2 or 3-ArC), 127.4 (2 or 3-ArC), 83.0 (Ar*C*H) and 56.7 (OMe); *m*/*z* (CI) 273.0942 ($[MH]^+$. $C_{16}H_{17}O_2S$ requires 273.0949) and 241 ($[MH]^+$ − MeOH, 100%).

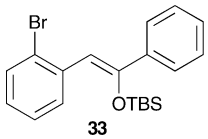
A similar experiment, but using sulfur dibenzotriazole (990 mg, 3.75 mmol) as the electrophile, yielded (1*R*,2*R*)-1,2-diphenylethane-1,2-dimethoxyethane as a powder (88.6 mg, 29.3%); mp 93–95 °C (from petroleum ether) (lit.,[38] 94–95 °C); $[\alpha]_D^{22}$ +90 (*c* 1.00 in EtOH); δ_H(300 MHz; $CDCl_3$) 7.18–7.12 (6 H, m, ArH), 7.02–6.95 (4 H, m, ArH), 4.30 (2 H, s, ArC*H*) and 3.26 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 138.1 (1-ArC), 127.9 (ArC), 127.8 (ArC), 127.5 (ArC), 87.7 (Ar*C*H) and 57.2 (OMe), and *sulfide* **212** as a powder (53.0 mg, 15.6%).

(10*R*,11*R*)-10,11-Di(methoxymethoxy)-10,11-dihydrodibenzo-[*b*,*f*]thiepine 23. Acetal **9** (538 mg, 1.17 mmol) was reacted according to **method D** using sulfur diimidazole (1.16 g, 7.02 mmol) as the electrophile. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate, yielded the *sulfide* as an oil (139 mg, 35.8%); $[\alpha]_D^{22}$ +0.9 (*c* 4.82 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2823 (CO), 1590 (Ar), 1567 (Ar) and 701 (C–S); δ_H(300 MHz; $CDCl_3$) 7.52 (2 H, dd, *J* 7.7 and 1.2, 1 or 4-ArH), 7.47 (2 H, dd, *J* 7.7 and 1.5, 1 or 4-ArH), 7.26 (2 H, td, *J* 7.7 and 1.3, 2 or 3-ArH), 7.11 (2 H, td, *J* 7.7 and 1.5, 2 or 3-ArH), 5.45 (2 H, s, ArC*H*), 4.97 (2 H, d, *J* 6.8, OCH_ACH_BO), 4.74 (2 H, d, *J* 6.8, OCH_ACH_BO), and 3.42 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 139.1 (4a or 11a-ArC), 136.5 (4a or 11a-ArC), 132.4 (1 or 4-ArC), 130.8 (1 or 4-ArC), 127.9 (2 or 3-ArC), 127.3 (2 or 3-ArC), 96.1 (OCH_2O), 80.1 (Ar*C*H) and 56.0 (OMe); *m*/*z* (EI) 332.1083 (M^+. $C_{18}H_{20}O_4S$ requires 332.1082), 301 (M^+ − MeOH, 15%), 271 (M^+ − CH_3OCH_2OH, 86) and 197 (100).

(10*R*,11*R*)-10,11-Dimethylmethylenedioxy-10,11-dihydrodibenzo[*b*,*f*]thiepine 22. Dioxolane **6** (500 mg, 1.76 mmol) was reacted according to **method D** using sulfur diimidazole (1.75 g, 10.56 mmol) as the electrophile. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate, yielded the *sulfide* as a powder (41.4 mg, 12.0%); mp 42–44 °C; $[\alpha]_D^{22}$ −22.0 (*c* 1.00 in CH_2Cl_2); ν_{max}(CH_2Cl_2)/cm^{-1} 1593 (Ar), 1566 (Ar) and 1126 (CO); δ_H(300 MHz; $CDCl_3$) 7.60 (2 H, dd, *J* 7.7 and 1.5, 1 or 4-ArH), 7.43 (2 H, dd, *J* 7.7 and 1.2, 1 or 4-ArH), 7.28 (2 H, td, *J* 7.7 and 1.5, 2 or 3-ArH), 7.19 (2 H, td, *J* 7.7 and 1.6, 2 or 3-ArH), 5.23 (2 H, s, ArC*H*) and 1.62 (6 H, s, C(Me)$_2$); δ_C(75.5 MHz; $CDCl_3$) 138.4 (4a or 11a-ArC), 135.0 (4a or 11a-ArC), 129.3 (1 or 4-ArC), 127.6 (2 or 3-ArC), 127.3 (2 or 3-ArC), 126.4 (1 or 4-ArC), 109.6 (OCO), 78.7 (Ar*C*H) and 27.1 (C(*C*H$_3$)$_2$); *m*/*z* (EI) 284.0875 (M^+. $C_{17}H_{16}O_2S$ requires 284.0871), 226 (M^+ − $(Me)_2CO$, 81%), and 197 (100).

(10*R*,11*R*)-10,11-Bis[(1,1-dimethylethyl)dimethylsiloxy]-10,11-dihydrodibenzo[*b*,*f*]thiepine 21. Disilyl ether **7** (800 mg, 1.33 mmol) was reacted according to **method D** using sulfur diimidazole (1.33 g, 8.00 mmol) as the electrophile. Purification by flash chromatography (loaded as a solution in petroleum ether), eluting with petroleum ether–ethyl acetate, and recrystallisation from petroleum ether yielded the *sulfide* as needles (118 mg, 18.8%); mp 90–91.5 °C (from petroleum ether); $[\alpha]_D^{22}$ +3.3 (*c* 1.00 in CH_2Cl_2); ν_{max}(CH_2Cl_2)/cm^{-1} 1589 (Ar), 1564 (Ar), 1434 (Si–CH_3), 1265 (Si–CH_3), and 705 (C–S); δ_H(300 MHz; $CDCl_3$) 7.79 (2 H, dd, *J* 7.6 and 1.0, 1 or 4-ArH), 7.49 (2 H, dd, *J* 7.6 and 1.4, 1 or 4-ArH), 7.40 (2 H, td, *J* 7.6 and 1.4, 2 or 3-ArH), 7.26 (2 H, td, *J* 7.6 and 1.3, 2 or 3-ArH), 5.12 (2 H, s, Ar*C*H), 0.79 (2 H, s, C(Me)$_3$), 0.34 (6 H, s, SiMe_AMe$_B$) and 0.13 (6 H, s, SiMe$_A$$Me_B$); δ_C(75.5 MHz; $CDCl_3$) 149.2 (4a or 11a-ArC), 136.4 (1 or 4-ArC), 136.3 (4a or 11a-ArC), 129.8 (2 or 3-ArC), 126.8 (2 or 3-ArC), 126.6 (1 or 4-ArC), 74.7 (Ar*C*H), 27.0 (C(*C*H$_3$)$_3$), 17.5 (*C*(Me)$_3$), −2.4 (SiMe_AMe$_B$) and −2.9 (SiMe$_A$$Me_B$); *m*/*z* (CI) 473.2362 ($[MH]^+$. $C_{26}H_{41}O_2SSi_2$ requires 473.2366) and 205 (100%), 1-(2-bromophenyl)-2-phenyl-1-[(1,1-dimethylethyl) dimethylsiloxy]ethylene **33** as a yellow oil (43.9 mg, 8.5%); ν_{max}(film)/cm^{-1} 3054 (C=C–H), 2955 (SiC–H$_3$), 2928 (SiC–H$_3$), 1585 (Ar), 1557 (Ar) and 1361 (CMe$_3$); δ_H(300 MHz; $CDCl_3$) 7.72 (1 H, br d, *J* 7.7, ArH), 7.59 (2 H, td, *J* 8.0 and 1.3, ArH), 7.53 (1 H, dd, *J* 7.9 and 1.3, ArH), 7.44–7.23 (3 H, m, ArH), 7.32 (1 H, s, ArCH), 7.11 (1 H, br d, *J* 7.6 and 1.6, ArH), 0.92 (9 H, s, C(Me$_3$)$_3$ and 0.39 (6 H, s, Si(CH$_3$)$_2$); δ_C(75.5 MHz; $CDCl_3$) 143.3 (ArC), 137.4 (ArC), 136.8 (ArC), 136.3 (ArC), 133.9 (ArC), 133.2 (ArC), 128.6 (ArC), 128.3 (ArC), 128.2 (ArC), 127.6 (Ar*C*H), 126.7 (ArC), 126.3 (ArC), 126.0 (ArC), 124.2 (ArC), 27.0 (C(*C*H$_3$)$_3$), 18.0 (*C*(Me)$_3$) and −2.9 (Si(Me)$_2$); *m*/*z* (CI) 389.0941 ($[MH]^+$. $C_{20}H_{26}OBrSi$ requires 389.0936), 359 ($[MH]^+$ − 2 × Me, 10%), 317 ($[MH]^+$ − $OSi(Me)_2$, 61), and 73 (100), and another unidentified compound as plates (35 mg); mp 107–108.5 °C (from petroleum ether); $[\alpha]_D^{22}$ −44.5 (*c* 1.00 in CH_2Cl_2); ν_{max}(CH_2Cl_2)/cm^{-1} 3427, 1591, 1586, 1434, 1265,

657; δ_H(300 MHz; $CDCl_3$)* 7.80 (2 H, br d, *J* 7.8), 7.51–7.46 (2 H, m), 7.42 (1 H, td, *J* 7.5 and 1.5), 7.35 (1 H, dd, *J* 7.5 and 1.2), 7.30 (1 H, dd, *J* 7.5 and 1.2), 7.13 (1 H, td, *J* 7.9 and 1.6), 5.31 (1 H, d, *J* 4.1), 5.15 (1 H, d, *J* 4.1), 0.82 (9 H, s), 0.32 (3 H, s) and 0.13 (3 H, s); δ_C(75.5 MHz; $CDCl_3$) 127.8, 127.5, 127.1, 126.3, 123.9, 75.3, 75.1, 27.0, 17.6, −2.1 and −2.9 *m*/*z* (CI) 505.1545 ($[MH]^+$. $C_{25}H_{37}O_1S_3Si_2$ requires 505.1541), 391 (50%), 381 (48), 333 (91), 331 (86) and 73 (100).



33

10,11-Dihydrodibenzo[*b*,*f*]thiepine 26. Bibenzyl **25** (2.10 g, 6.18 mmol) was reacted according to **method E** using sulfur diimidazole (6.16 g, 37.9 mmol) as the electrophile. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallisation from petroleum ether yielded the sulfide as yellow needles (34.0 mg, 2.6%); mp 47–48 °C (from petroleum ether) (lit.,[39] 47–50 °C); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1584 (Ar), 1571 (Ar) and 703 (C–S); δ_H(300 MHz; $CDCl_3$) 7.45 (2 H, dd, *J* 7.9 and 1.1, 4-ArH), 7.20–6.87 (6 H, m, ArH) and 3.04–2.92 (4 H, m, $CH_AH_{A'}CH_BH_{B'}$).

Reactions of diphenyl sulfide

Methyldiphenylsulfonium tetrafluoroborate. Diphenyl sulfide (0.41 ml, 2.46 mmol) was stirred with silver tetrafluoroborate (0.50 g, 2.46 mmol) in acetonitrile (2 ml) for 1 h. The suspension was cooled to 0 °C before the dropwise addition of methyl iodide (0.48 ml, 7.38 mmol). The reaction was stirred at room temperature for 48 h. The suspension was filtered and the filtrate concentrated under reduced pressure. Trituration with diethyl ether (5 ml) yielded the salt as off-white platelets (300 mg, 42.3%); mp 61–63 °C (from diethyl ether) (lit.,[40] 61–62 °C); δ_H(300 MHz; DMSO) 7.39–7.25 (10 H, m, ArH) and 3.30 (3 H, s, SCH_3); δ_F(282.65 MHz, DMSO) −147.9 (s, BF_4).

Methyldiphenylsulfonium trifluoromethanesulfonate. Methyl trifluoromethanesulfonate (1.36 ml, 12.0 mmol) was added dropwise to a solution of diphenyl sulfide (1.0 ml, 6.0 mmol) in dry dichloromethane (10 ml) under an argon atmosphere. The reaction was stirred at room temperature for 48 h. Then 1.25 M sodium hydroxide (15 ml) was added and the solution stirred overnight. The layers were separated and the aqueous layer extracted with dichloromethane (3 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallisation from ethanol yielded the salt as platelets (1.94 g, 92.4%); mp 95–96.5 °C (from ethanol) (lit.,[41] 94–97.5 °C); δ_H(300 MHz; DMSO) 7.47–7.32 (10 H, m, ArH) and 3.23 (3 H, s, SMe); δ_F(282.65 MHz, DMSO) −77.7 (s, CF_3).

Diphenyl-*N*-*p*-tosylsulfimide. Diphenyl sulfide (0.50 ml, 3.01 mmol) and the tetrabutylammonium salt of chloramine-T (1.42 g, 3.01 mmol) were dissolved in dichloromethane (30 ml) and the solution heated to 40 °C. The reaction was stirred at this temperature for 5 h. The solution was allowed to cool to room temperature, washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was recrystallised from methanol to yield the sulfimide as needles (773 mg, 72.5%); mp 123–124 °C (from methanol) (lit.,[42] 113 °C); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1556 (Ar) and 930 (S=N); δ_H(300 MHz; $CDCl_3$) 7.75 (2 H, d, *J* 8.1, SO_2ArH), 7.65–7.58 (4 H, m, ArH), 7.53–7.40 (6 H, m, ArH), 7.14 (2 H, d, *J* 8.1, SO_2ArH) and 2.33 (3 H, s, SO_2ArCH_3); δ_C(75.5 MHz; $CDCl_3$) 141.7 (ArC), 141.3 (ArC), 136.5 (ArC), 132.3 (ArC), 129.9 (ArC), 129.1 (ArC), 127.2 (ArC), 126.3 (ArC) and 21.4 ($ArCH_3$).

In a similar experiment diphenyl sulfide (0.50 ml, 3.01 mmol) was reacted with chloramine-T trihydrate to yield the sulfimide as needles (64.0 mg, 6.0%).

In another experiment, to a solution of copper triflate benzene complex (333 mg, 0.663 mmol, 25 mol%) in dry acetonitrile (10 ml) was added PhI=NTs (1.09 g, 2.92 mmol) under an argon atmosphere. Then diphenyl sulfide (0.44 ml, 2.65 mmol) was added and the solution stirred at room temperature for 48 h. Water (10 ml) was added, the layers separated and the aqueous layer extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluting with petroleum ether–ethyl acetate, to yield the sulfimide as needles (586 mg, 62.4%).

Diphenyl sulfimine. Diphenyl-*N*-*p*-tosylsulfimine (250 mg, 70.4 mmol) was dissolved in concentrated sulfuric acid (1 ml). As soon as the sulfimide dissolved the solution was poured into ice water (10 ml) and sodium hydroxide solution (10 ml) added until the solution became alkaline. The solution was extracted with chloroform (2 × 5 ml) and concentrated under reduced pressure. The residue was once again dissolved in concentrated sulfuric acid (5 ml). The solution was decolourised with charcoal and sodium hydroxide added until the solution became alkaline whereupon the product precipitated out of solution. The suspension was filtered to yield the free sulfimide as needles (131 mg, 93.2%); mp 56–59 °C (from toluene) (lit.,[18] 74 °C); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1557 (Ar) and 934 (S=N); δ_H(300 MHz; $CDCl_3$) 7.65–7.40 (m, ArH); δ_C(75.5 MHz; $CDCl_3$) 145.5 (ArC), 141.1 (ArC), 131.0 (ArC), 131.0 (ArC), 130.4 (ArC), 129.3 (ArC), 129.3 (ArC), 129.2 (ArC), 125.9 (ArC) and 124.7 (ArC).

Diphenylsulfoxamide (2,4,6-trimethyl)phenylsulfonate. Diphenyl sulfoxide (500 mg, 0.0248 mmol) was dissolved in dry dichloromethane (20 ml). MSH (800 mg, 37.1 mmol) was added and the reaction stirred at room temperature overnight. The residue was washed with water (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was triturated with diethyl ether (5 ml) and filtered to yield the aminated sulfide as a gum (806 mg, 78.1%); mp 169–173 °C (lit.,[43] 179–183 °C); δ_H(300 MHz; DMSO) 7.40 (4 H, dd, *J* 7.9 and 3.6, ArH), 7.27–7.24 (6 H, m, ArH), 6.67 (2 H, s, $(CH_3)_3ArH$), 2.43 (6 H, s, $ArCH_3$) and 2.07 (6 H, s, $ArCH_3$).

Reactions of thiepines

(10*R*,11*R*)-4,6-Difluoro-10,11-dimethoxy-10,11-dihydrodibenzo-[*b*,*f*]thiepine 5-oxide 27. Sulfide **14** (30 mg, 0.097 mmol) was dissolved in dichloromethane (10 ml). 57–86% *m*-CPBA (32.4 mg) was dissolved in dichloromethane (5 ml) and dried ($MgSO_4$)

* Coupling constants verified by comparison to a spectrum of the compound run at 400 MHz.

before its addition to the reaction solution. The reaction was stirred at room temperature for 2 h. Then 1.25 M sodium hydroxide (10 ml) was added and the reaction stirred for a further 1 h. The layers were separated and the aqueous layer extracted with dichloromethane (3 × 30 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallisation from petroleum ether yielded the *sulfoxide* as a powder (31.0 mg, 99%) (characterised in a previous experiment).

2-Diazomalonic acid dimethyl ester 29. Dimethylmalonate (5.36 g, 40.6 mmol), triethylamine (5.7 ml, 41.2 mmol) and tosyl azide (8.0 g, 40.6 mmol) were dissolved in acetonitrile (60 ml). The solution was stirred at room temperature overnight. The solution was concentrated under reduced pressure, partitioned between dichloromethane (100 ml) and water (100 ml) and the resulting mixture stirred for 1 h at room temperature. The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate, yielded the diazomalonate as a yellow oil (5.33 g, 83.1%); δ_H(300 MHz; $CDCl_3$) 3.85 (s, OMe); *m*/*z* (CI) 159 ([MH]$^+$, 35%), 127 ([MH]$^+$ − MeOH, 32) and 101 ([MH]$^+$ − CO_2Me, 100).

(10*R*,11*R*)-10,11-Dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepine-5-ylidene malonic acid dimethyl ester 30. Sulfide **15** (600 mg, 2.21 mmol) and diazodimethylmalonate **29** (418 mg, 2.65 mmol) were dissolved in dichloromethane (20 ml). Rhodium(II) acetate (49 mg, 0.111 mmol, 5 mol%) was added and the reaction stirred at room temperature for 72 h. The reaction was washed with a saturated sodium chloride solution (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was subsequently purified by flash chromatography, eluting with ethyl acetate. The crude material was dissolved in a minimum amount of ethyl acetate (4 ml) and the impurities reprecipitated by the addition of petroleum ether (15 ml). The suspension was filtered and the filtrate concentrated under reduced pressure to yield the *sulfonium ylide* as a powder (662 mg, 74.6%); mp 203–204 °C (from petroleum ether–ethyl acetate); $[a]_D^{22}$ −118 (*c* 1.00 in CH_2Cl_2); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2951 (COO–CH_3), 2830 (C–O ether), 1716 (C=O), 1475 (OCH_2), 1434 (OCH_2) and 704 (C–S); δ_H(300 MHz; $CDCl_3$) 7.77 (1 H, br d, *J* 8.5, ArH), 7.70 (1 H, br d, *J* 8.1, ArH), 7.53–7.35 (6 H, m, ArH), 5.07 (1 H, d, *J* 7.9, ArCH_A), 4.82 (1 H, d, *J* 7.9, ArCH_B), 3.62 (6 H, br s, CO_2Me) and 3.30 (6 H, s, OMe); δ_C(75.5 MHz; $CDCl_3$) 166.8 (CO_2Me), 136.2 (4a or 5a-ArC), 135.5 (4a or 5a-ArC), 133.1 (ArC), 132.8 (ArC), 130.2 (ArC), 128.9 (ArC), 127.1 (ArC), 126.7 (ArC), 83.8 (ArC_AH), 80.8 (ArC_BH), 57.4 (OC_AH_3), 57.0 (OC_BH_3), 55.1 (SC(CO_2Me)$_2$) and 51.1 (CO_2CH_3); *m*/*z* (CI) 403.1207 ([MH]$^+$. $C_{21}H_{23}O_6S$ requires 403.1207), 371 ([MH]$^+$ − MeOH, 100%), 339 ([MH]$^+$ − 2 × MeOH, 12) and 271 ([MH]$^+$ − $H_2C(CO_2Me)_2$, 72).

2-Diazamalonic acid dibenzyl ester. Dibenzylmalonate (12.5 g, 47.7 mmol) was reacted in a similar way to dimethylmalonate. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate, yielded the diazomalonate as an off-white powder (12.1 g, 88.1%); δ_H(300 MHz; $CDCl_3$) 7.39–7.30 (5 H, m, ArH), 5.27 (2 H, s, ArCH); *m*/*z* (EI) 181 (M$^+$ − BnOH, 12%), 107 (BnO, 46) and 91 (Bn, 100).

(10*R*,11*R*)-10,11-Dimethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepine-5-ylidene malonic acid dibenzyl ester 32. Sulfide **15** (1.21 g, 4.45 mmol) and diazodibenzylmalonate (1.49 g, 5.34 mmol) were reacted using a similar method to that used in the synthesis of the ylide **30**. The crude mixture was subsequently purified by flash chromatography, eluting with ethyl acetate. The product was dissolved in a minimum amount of ethyl acetate (10 ml) and the impurities reprecipitated by the addition of petroleum ether (50 ml). The suspension was filtered and the filtrate concentrated under reduced pressure to yield the *sulfonium ylide* as a powder (1.69 g, 67.7%); mp 117–118 °C (from petroleum ether–ethyl acetate); $[a]_D^{22}$ −9 (*c* 1.00 in CH_2Cl_2); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2820 (CO), 1717 (C=O), 1557 (Ar), 1519 (Ar) and 1454 (OCH_2); δ_H(300 MHz; $CDCl_3$) 7.78 (1 H, d, *J* 7.9, ArH), 7.69 (1 H, d, *J* 7.8, ArH), 7.46 (2 H, td, *J* 7.4 and 1.1, ArH), 7.41 (2 H, td, *J* 7.4 and 1.1, ArH), 7.33–7.27 (2 H, m, ArH), 7.19 (10H, m, *exo*-ArH), 5.11 (4 H, br s, OCH_2Bn), 5.02 (1 H, d, *J* 7.7, ArCH_A), 4.79 (1 H, d, *J* 7.7, ArCH_B), 3.34 (3 H, s, OMe_A) and 3.22 (3 H, s, OMe_B); δ_C(75.5 MHz; $CDCl_3$) 166.8 (CO_2Bn), 137.2 (*ipso*-ArC), 136.1 (4a or 5a-ArC), 135.5 (4a or 5a-ArC), 133.2 (ArC), 132.7 (ArC), 132.6 (ArC), 130.7 (ArC), 130.2 (ArC), 128.9 (ArC), 128.1 (*exo*-ArC), 127.6 (ArC), 127.3 (ArC), 127.2 (*exo*-ArC), 126.9 (ArC), 83.7 (ArC_AH), 80.8 (ArC_BH), 65.2 (OCH_2Bn), 57.5 (OC_AH_3), 56.9 (OC_BH_3) and 55.0 (SC(CO_2Me)$_2$); *m*/*z* (CI) 555.1850 ([MH]$^+$. $C_{33}H_{31}O_6S$ requires 555.1841), 447 ([MH]$^+$ − BnOH, 28%), 241 ([MH]$^+$ − $CH_2(CO_2Bn)_2$, 58) and 91 (Bn, 72).

9-(1,3-Dioxolane)-9*H*-thioxanthene 24. Dioxolane **22** (137 mg, 0.413 mmol) was dissolved in ethylene gylcol (5 ml). Toluene-*p*-sulfonic acid (156 mg, 0.907 mmol) was added and the solution heated to 80 °C. The reaction was stirred at this temperature overnight. The solution was allowed to cool to room temperature, washed with water (5 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate, and recrystallisation from petroleum ether yielded the *sulfide* as a powder (76.1 mg, 68.3%); mp 160–161 °C (from petroleum ether); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2891 (CO), 1616 (Ar) and 1588 (Ar); δ_H(300 MHz; $CDCl_3$) 7.40–7.35 (4 H, m, ArH), 7.26–7.21 (4 H, m, ArH), 5.21 (1 H, dd, *J* 6.6, ArCH), 4.13 (1 H, dd, *J* 6.6, CH($OCH_2)_2$) 3.91–3.81 (2 H, m, OCH_AH$_B$C$H_{A'}$H$_{B'}$O) and 3.79–3.76 (2 H, m, OCH$_A$$H_BCH_{A'}$$H_{B'}$O); δ_C(75.5 MHz; $CDCl_3$) 133.1 (4a or 10a-ArC), 132.6 (4a or 10a-ArC), 130.7 (ArC), 127.4 (ArC), 126.5 (ArC), 126.3 (ArC), 101.9 (ArCH), 65.2 (CH_2CH_2) and 53.9 ($CH(OCH_2)_2$); *m*/*z* (EI) 270.0710 (M$^+$. $C_{15}H_{14}O_2S$ requires 270.0715), 197 (M$^+$ − $CH(OCH_2)_2$, 88%) and 73 (100).

Acknowledgements

Andrew Hudson thanks the Univerisity of Bristol for a University Scholarship. Hirihattaya Phetmung thanks the Royal Thai Government for a Scholarship. Paul Wyatt thanks the School of Chemistry for generous support.

References

1 M. Provita, M. Jilek, M. Rajsner, J. Pomykacek, M. Ryska, J. Holubek, E. Svatek and J. Metysova, *Collect. Czech. Chem. Commun.*, 1986, **51**, 698.

2 K. Sindelar, J. Jilek, J. Pomykacek, V. Valenta, M. Hrubantova, M. Vlkova, J. Holubek, E. Svatek, M. Ryska, J. Metysova and M. Provita, *Collect. Czech. Chem. Commun.*, 1990, **55**, 2282.
3 A. Hudson, A. G. Orpen, H. Phetmung and P. Wyatt, *Tetrahedron Lett.*, 1999, **40**, 813–816.
4 J. O. Jilek, E. Svatek, J. Metysova, J. Pomykacek and M. Provita, *Collect. Czech. Chem. Commun*, 1967, **32**, 3186.
5 G. P. Scott, *J. Am. Chem. Soc.*, 1953, **75**, 6332.
6 H. W. Whitlock, *Tetrahedron Lett.*, 1961, 593.
7 J. Nakayama, T. Konishi, A. Ishii and M. Hoshino, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 2608–2612.
8 P. Wyatt, S. Warren, M. McPartlin and T. Woodroffe, *J. Chem. Soc., Perkin Trans. 1*, 2001, 279–297.
9 J. E. McMurry, *Chem. Rev.*, 1989, **89**, 1513–1524.
10 A. Fürstner and A. Hupperts, *J. Am. Chem. Soc.*, 1995, **117**, 4468–4475.
11 A. Terfort and H. Brunner, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1467–1479.
12 F. Fehér and B. Degen, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 703–704.
13 J. Sundberg, *J. Heterocycl. Chem.*, 1977, **14**, 517–518.
14 F. Belal, M. M. Hefnawy and F. A. Aly, *J. Pharm. Biomed. Anal.*, 1997, **16**, 369–367.
15 S. Warren and P. Wyatt, *J. Chem. Soc., Perkin Trans. 1*, 1998, 249–255.
16 M. Madesclaire, *Tetrahedron*, 1986, **42**, 5459.
17 T. Yamamoto, D. Yoshida, J. Hojyu and H. Teraughi, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 3341.
18 T. Yoshimura, T. Omata, N. Furukawa and S. Oae, *J. Org. Chem.*, 1976, **41**, 1728.
19 H. Takada, Y. Nishibayashi, K. Ohe and S. Uemura, *J. Chem. Soc., Chem. Commun.*, 1996, 931.
20 Y. Yamada, T. Yamamoto and M. Okawara, *Chem. Lett.*, 1975, 361.
21 E. S. Lewis, S. Edward, S. Kukes and C. D. Slater, *J. Am. Chem. Soc.*, 1980, **102**, 1619.
22 K. Fukui, K. Ohkubo and T. Yamabe, *Bull. Chem. Soc. Jpn.*, 1969, **42**, 312.
23 H. Meerwein, E. Battenberg, H. Gold, P. E and G. Willfang, *J. Prakt. Chem.*, 1939, **154**, 83.
24 Y. Tamura, K. Sumoto, H. Minamikawa, H. Taniguchi and M. Ikeda, *J. Org. Chem.*, 1973, **38**, 1239.
25 Y. Tamura, K. Sumoto, H. Minamikawa, H. Taniguchi and M. Ikeda, *J. Org. Chem.*, 1973, **38**, 4324.
26 J. Cuffe, R. J. Gillespie and A. E. A. Porter, *J. Chem. Soc., Chem. Commun.*, 1978, 641.
27 R. J. Gillespie and A. E. A. Porter, *J. Chem. Soc., Chem. Commun.*, 1979, 50.
28 The cyclopropane was suggested by NMR of crude material but purification was not successful and so this compound was not conclusively identified and characterised.
29 A. Banerji and G. P. Kalena, *Tetrahedron Lett.*, 1980, **21**, 3003–3304.
30 Our syntheses of *achiral* disulfides has been reported: P. Wyatt and A. Hudson, *Org. Biomol. Chem.*, 2004, **2**, 1528–1530.
31 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
32 K. Rafizadeh and K. Yates, *J. Org. Chem.*, 1984, **49**, 1500.
33 T. Mitsumori, N. Koga and H. Iwamura, *J. Phys. Org. Chem.*, 1994, **7**, 43.
34 T. R. Kelly, Q. Li and V. Bhushan, *Tetrahedron Lett.*, 1990, **31**, 161.
35 I. I. Lapkin, T. N. Povarnitsyna and L. A. Kostareva, *Zh. Obshch. Khim.*, 1969, **39**, 1460.
36 A. Terfort and H. Brunner, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1467.
37 W. H. Pirkle, D. L. Sikkenga and M. S. Pavlin, *J. Org. Chem.*, 1977, **42**, 384–387.
38 A. Merz, M. Eichner and R. Tomahogh, *Liebigs Ann. Chem.*, 1981, 1774.
39 M. Hori, T. Kataoka, H. Shimizu, M. Miyagaki and M. Murase, *Chem. Pharm. Bull.*, 1974, **22**, 2014.
40 T. Yamabe, *J. Org. Chem.*, 1971, **36**, 1971.
41 D. N. Kevill and S. W. Anderson, *J. Org. Chem.*, 1986, **51**, 5029.
42 A. Kucsman, I. Kapovits and M. Balla, *Tetrahedron*, 1962, **18**, 75.
43 Y. Tamura, K. Sumoto, J. Minamikawa and M. Ikeda, *Tetrahedron Lett.*, 1972, **40**, 4137.

