PERKIN 1

Synthesis and evaluation of a broad range of chiral sulfides for asymmetric sulfur ylide epoxidation of aldehydes

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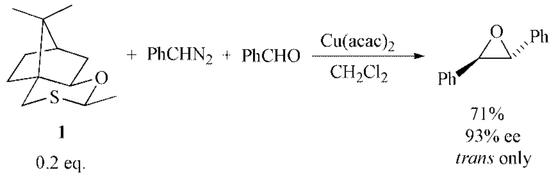
We have recently developed a catalytic, sulfur ylide mediated process for converting aldehydes into epoxides using benzaldehyde tosylhydrazone sodium salt which decomposes to generate phenyldiazomethane *in situ*. Although chiral 1,3-oxathianes gave good yields and excellent diastereo- and enantio-control when phenyldiazomethane was employed, only low yields were obtained when using the simplified procedure employing benzaldehyde tosylhydrazone sodium salt. Thus, a range of more robust chiral sulfides based on thianes, thiolanes, and 1,4-oxathianes were designed to achieve high yield and high enantioselectivity. The sulfides all possessed the following features: conformationally locked cyclic sulfide in which only one of the two lone pairs was accessible (not relevant for C_2 symmetric substrates); ylide conformation and face selectivity was to be controlled through non-bonded steric interactions. Chirality was introduced from chiral pool materials (camphor, amino acids, lactic acid, limonene, carvone, glyceraldehyde), through enzyme mediated reduction/hydrolysis and through the use of chiral reagents (hydroboration). The sulfide catalysts were tested in the reaction between benzaldehyde tosylhydrazone salt and benzaldehyde to give *trans*-stilbene oxide. The range of chiral sulfide catalysts derived from camphor gave *trans*-stilbene oxide in generally good yield (23–95%) and with moderate enantioselectivity (40–76% ee). The range of novel chiral thianes and 1,4-oxathianes gave *trans*-stilbene oxide again in generally good yield (9–92%) and with moderate enantioselectivity (20–77% ee). The range of C_2 symmetric chiral sulfide catalysts based on 5 and 6 membered rings gave *trans*-stilbene oxide in moderate yield (10–78%) and with variable enantioselectivity (8–87% ee). In none of the cases could high enantioselectivity and high yield be achieved simultaneously. Analysis of the results led us to the conclusion that the moderate enantioselectivity was a result of poor control in the ylide conformation and this led to the design of completely rigid [2.2.1] bicyclic sulfides which finally gave high enantioselectivity and high yield in the epoxidation process.

Introduction

The development of methods for the asymmetric synthesis of epoxides continues to warrant intense research effort, despite the seminal contributions of Sharpless,[1] Jacobsen,[2] Shi[3] and others.[4] We have focused on epoxidation of carbonyl compounds as a complementary method to the oxidative processes cited above.[5] Indeed, we have developed a catalytic, sulfur ylide mediated process operating under neutral conditions which, with 1,3-oxathiane **1**, gave good yields and excellent diastereo- and enantio-control (Scheme 1).[5,6] More recently, we have



Scheme 1

achieved a simplified process, whereby phenyldiazomethane is generated *in situ* from tosylhydrazone salt **2**, thus eliminating the need for the preparation and handling of this potentially explosive compound (Scheme 2).[5b,7] However, 1,3-oxathiane **1** proved to be unstable under these modified conditions, and only gave *trans*-stilbene oxide in low yield, albeit with high enantioselectivity.[5b] We therefore embarked on the preparation of a broader range of more stable chiral sulfide catalysts, for use

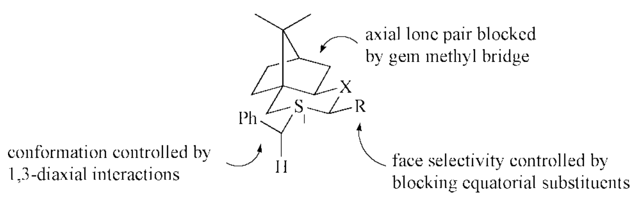


Fig. 1

in the new *in situ* process. In the design of new catalysts we were guided by our experiences using oxathiane **1**, from which we learnt that three features were required to achieve good enantiocontrol. These comprised: (i) formation of a single sulfur ylide by blocking one of the two sulfur lone pairs, (ii) control in the conformation of the ylide and (iii) control in the face selectivity of the ylide (Fig. 1).

In this paper we describe the synthesis of a broad range of sulfides, which fulfil these criteria, their application in epoxidation and how additional criteria were eventually required to finally arrive at sulfide catalysts which gave high enantioselectivity.

Results and discussion

Sulfides derived from camphor

We initially synthesized camphor derived sulfides **3**–**8** as it was felt that these would fulfil the three criteria required: the axial

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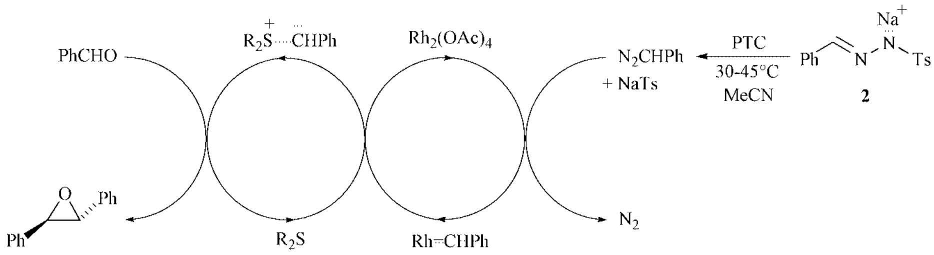
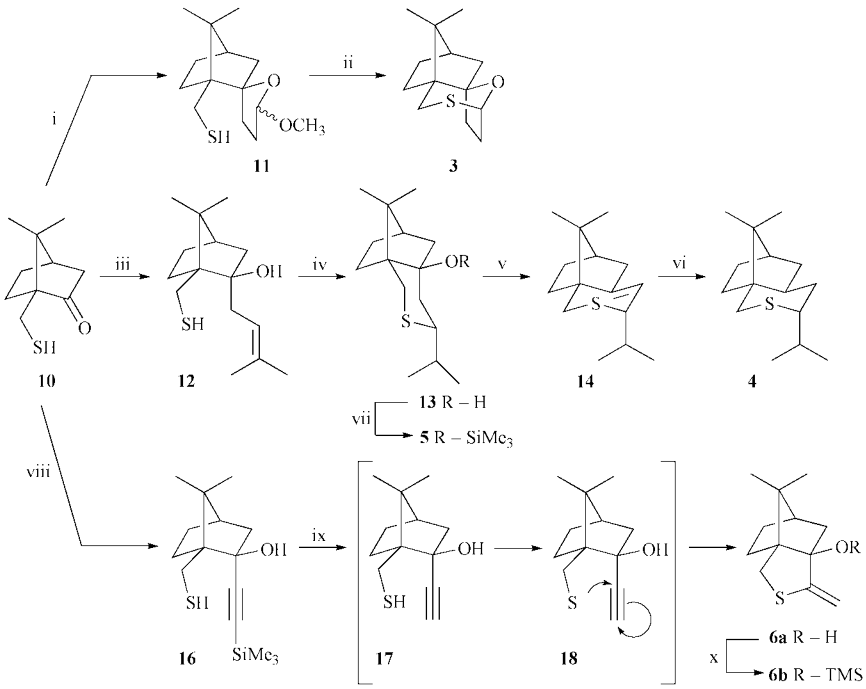


9%, 90% ee, *trans* only using **1**
95%, *trans* only using tetrahydrothiophene

Scheme 2



Scheme 3 *Reagents and conditions*: i $Br(CH_2)_2CH(OMe)_2$, Mg, THF, rt, then $CeCl_3$, THF, −78 °C, then **10**, THF, −78 °C to rt, 80%; ii BF_3·Et_2O, CH_2Cl_2, 0 °C, 40%; iii Li, naphthalene, THF, then $(CH_3)_2C$=$CHCH_2SPh$, then $CeCl_3$, 50%; iv AIBN, C_6H_6, 56%; v $(COCl)_2$, C_6H_6, 81%; vi H_2, Pd S/C, MeOH, 88%; vii *N*-trimethylsilylimidazole; viii $HCCSiMe_3$, *n*-BuLi, THF, 91%; ix TBAF, THF, 90%; x *N*-trimethylsilylimidazole, 94%.

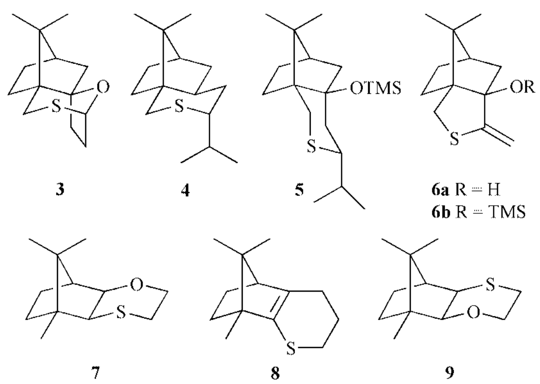
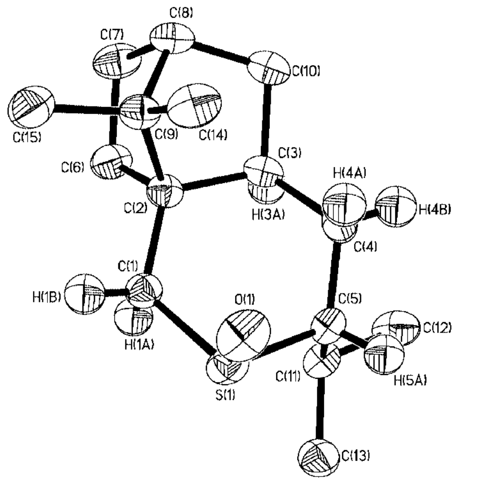


Fig. 2

lone pair would be blocked by the gem dimethyl bridge and ylide conformation and face selectivity would be controlled by non-bonding interactions, such as those shown for the generic sulfide structure in Fig. 1.

Sulfides **3**, **4**, **5**, **6a** and **6b** (Fig. 2) were prepared from their common precursor ketone **10**, readily available in one step from camphorsulfonyl chloride (Scheme 3).[8] The addition of the organocerium(III) reagent[9] generated by transmetallation of cerium chloride with the Grignard reagent derived from 1-bromo-3,3-dimethoxypropane,[10] to the sterically hindered mercaptoketone **10** provided the bicyclic compound **11** as a 70 : 30 mixture of acetal diastereoisomers. The formation of **11** resulted from an intramolecular transacetalization between the ketal group of the organocerium reagent and the *exo* alcohol obtained after addition of this organometallic reagent into the ketone. When **11** was treated with BF_3·Et_2O, formation of the third cycle occurred to afford the expected sulfide **3**. The synthesis of sulfide **4** proceeded from the regio- and stereoselective addition to ketone **10** of the allylcerium reagent, derived from 3,3-dimethylprop-2-enyl phenyl sulfide by the method of Cohen,[11] which afforded the *exo* alcohol **12** in 50% yield. Radical cyclisation of the thiol onto the pendant alkene in **12** was achieved using catalytic AIBN, giving hydroxy sulfide **13**. Attempts to remove the hydroxy group of **13** using the radical decomposition of the mixed oxalate ester with *N*-hydroxypyridine-2-thione were unsuccessful, as initial treatment with oxalyl chloride resulted in rapid elimination to give the unsaturated sulfide **14**.[12] However, we were able to use this material as hydrogenation afforded the target sulfide **4** diastereomerically pure. X-Ray crystallographic analysis of the corresponding sulfoxide **15** (prepared from **4** with MCPBA, 92%) (Fig. 3) revealed that the isopropyl substituent occupied the axial position in the thiane ring. Treatment of alcohol **13** with *N*-trimethylsilylimidazole provided sulfide **5**. Sulfides **6a** and **6b** were prepared from the addition of lithium trimethylsilylacetylide to ketone **10** to give *exo* alcohol **16** in good yield. Treatment of **16** with tetrabutylammonium fluoride gave the thiolane **6a**. This product is presumed to arise from initial desilylation of **16** to give anion **17**, which undergoes proton transfer to form thiolate **18** (the p*K*a of the thiol is 10–11 com-



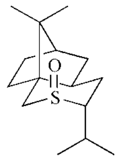


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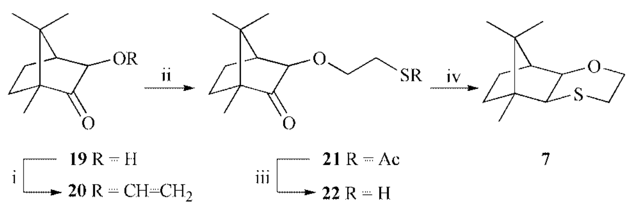
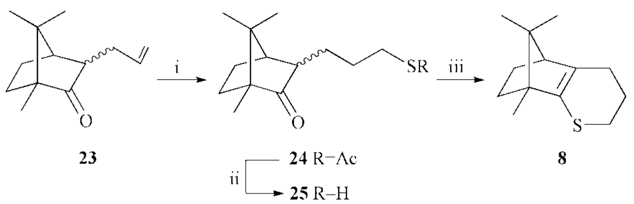
Fig. 3 ORTEP drawing of sulfoxide **15**.

pared with the p*K*a of the acetylene of 25). Ring closure of the thiolate onto the acetylene provides thiolane **6a** after protic work up.[13] Sulfide **6b** was obtained from **6a** by treatment with *N*-trimethylsilylimidazole.

The remaining target sulfides, **7** and **8**, were both obtained from camphor derivatives (Schemes 4 and 5). It should be noted



Scheme 4 *Reagents and conditions*: i EtOCH=CH$_2$, Pd(OAc)$_2$, phenanthroline, CH$_2$Cl$_2$, 40%; ii AcSH, AIBN, *hν*, C$_6$H$_6$; iii LiOH·H$_2$O, MeOH; iv BF$_3$·OEt$_2$, Et$_3$SiH, CH$_2$Cl$_2$, 52% over three steps.



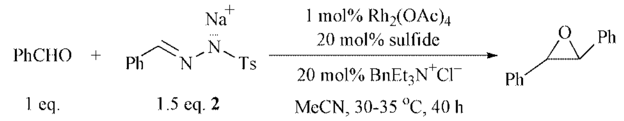
Scheme 5 *Reagents and conditions*: i AcSH, AIBN, C$_6$H$_6$; ii LiOH·H$_2$O, MeOH; iii BF$_3$·OEt$_2$, Et$_3$SiH, CH$_2$Cl$_2$, 63% over three steps.

that oxathiane **9**, which has the sulfur and oxygen atoms transposed, had been prepared previously and tested in our epoxidation process but gave only moderate enantioselectivity (Fig. 2) (Table 1, entry 9).[14] It was felt that oxathiane **7** would provide higher face selectivity in the ylide reaction than **9** because of the blocking methyl substituent and thereby lead to higher enantioselectivity. 1,4-Oxathiane **7** was prepared in four steps starting from *exo*-hydroxy camphor **19**[15] (Scheme 4), which was converted to the vinyl ether **20** using a Pd(OAc)$_2$–phenanthroline catalyst.[16] Radical addition of thioacetic acid to the terminal alkene in **20** was achieved with catalytic AIBN and under irradiation. Performing the same reaction only in the presence of AIBN did afford **21** in lower yield, but it was also less pure. Hydrolysis of thioacetate **21** was followed by cyclisation of thiol **22** with boron trifluoride–diethyl ether and triethylsilane to give 1,4-oxathiane **7**.[17] A similar procedure was implemented to prepare the unsaturated sulfide **8** (Scheme 5). Radical addition of the thioacetic acid to allylcamphor **23**[18] (7 : 3 *exo* : *endo*), followed by hydrolysis and subsequent cyclisation with boron trifluoride–diethyl ether afforded sulfide **8** in good overall yield. We were not able to reduce the double bond in sulfide **8** but it was nevertheless tested as a potential catalyst.

Table 1 Yields and enantioselectivities for epoxidation

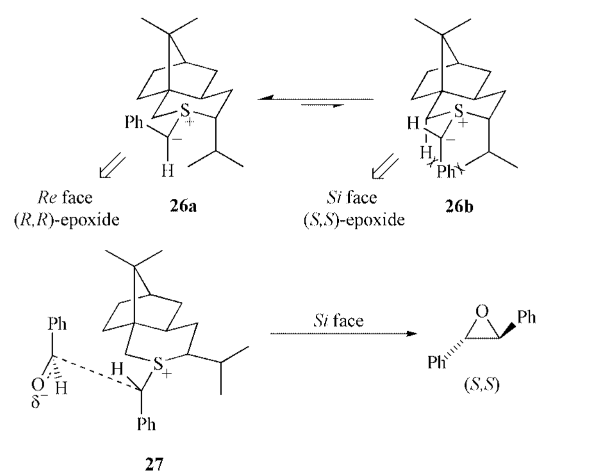
Entry	Sulfide	Yield (%)[a]	*trans* : *cis*[b]	ee (%)[c]
1	**1**	9	98 : 2	90 (*R*,*R*)
2	**3**	10	95 : 5	12 (*R*,*R*)
3	**4**	83	95 : 5	40 (*S*,*S*)
4	**5**	42	95 : 5	30 (*S*,*S*)
5	**6a**	23	57 : 43	63 (*R*,*R*)
6	**6b**	78	85 : 15	76 (*R*,*R*)
7	**7**	95	92 : 8	45 (*S*,*S*)
8	**8**	62	93 : 7	72 (*S*,*S*)
9	**9**	100	84 : 16	64 (*R*,*R*)

[a] Isolated yield. [b] By ^{1}H NMR. [c] Measured on a Chiralcel OD column.



Scheme 6

Results of epoxidation. Sulfides **3**–**8** were tested in the catalytic cycle with benzaldehyde, using the new *in situ* conditions (Scheme 6, Table 1). The bridged 1,3-oxathiane **3** was expected to be more robust to the reaction conditions than 1,3-oxathiane **1** (entry 1) as there is no longer the entropic driving force for hydrolysis. However, in the event, 1,3-oxathiane **3** behaved similarly to 1,3-oxathiane **1**, providing only a low yield of stilbene oxide but also with very low enantioselectivity (entry 2). The low enantioselectivity relative to **1** is probably due to replacement of the equatorial methyl group for a proton. However, as the yield was low, further work with 1,3-oxathianes was terminated[19] and alternative chiral sulfides **4**–**8** were prepared and tested in the epoxidation process. As expected, by comparison with 1,3-oxathiane **1**, sulfides **4**–**8** were significantly more robust in the *in situ* reaction conditions and gave substantially higher yields in all cases. However, in no case did the enantioselectivities obtained with catalysts **4**–**8** approach those afforded by 1,3-oxathiane **1**. The most likely explanation for this is incomplete control of ylide conformation, as illustrated for sulfide **4** (Scheme 7). The ylide formed from reaction of



Scheme 7

the more sterically accessible equatorial lone pair can adopt conformations **26a** or **26b**, but **26a** should be favoured due to 1,3-diaxial interactions in **26b**. The facial selectivity of **26a** should dictate that benzaldehyde attacks the *Re* face of the ylide, affording (*R*,*R*)-epoxide. However, this was not the sense of asymmetric induction observed. NOE experiments on **4** revealed that it preferred to adopt the boat conformation, presumably to avoid the 1,3-diaxial interactions between the

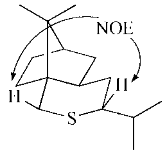


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Fig. 4

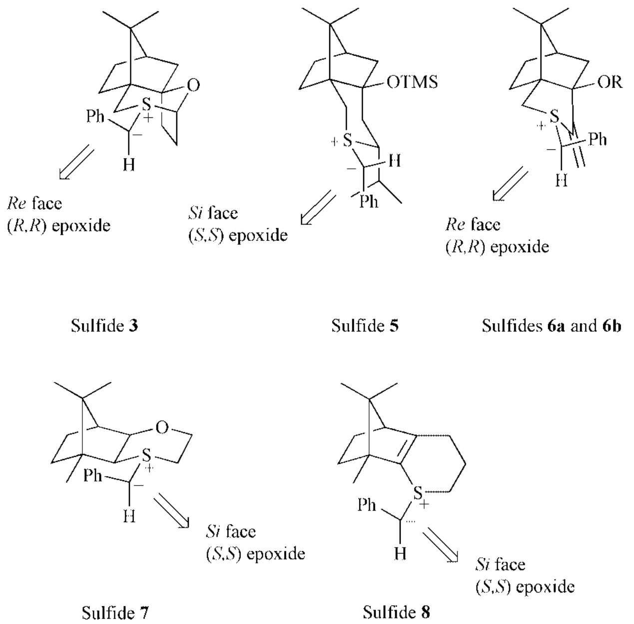


Fig. 5

proton and isopropyl group on the thiane ring (Fig. 4). Ylide **27**, formed from the boat conformation of **4** should then adopt the conformation shown and the *Si* face selectivity leads to the observed (*S*,*S*)-product. Similar arguments can be advanced for the observed absolute stereochemistry of the *trans*-stilbene oxide obtained from sulfides **5**, **6**, **7** and **8** (entries 4–8), with the major ylide conformation and facial selectivity shown in Fig. 5. Whilst we were able to account for the sense of asymmetric induction observed, we were surprised at the low level of enantioselectivity and particularly surprised that sulfide **7** only gave 45% ee in the epoxidation reaction as: (i) only one of the two lone pairs should react, (ii) the ylide conformation should be controlled by 1,3-diaxial interactions and (iii) the face selectivity of the ylide should be completely controlled. As points (i) and (iii) should be completely controlled, it must be ylide conformation that is poorly controlled.

These results demonstrated the need to simultaneously control the formation of a single diastereomeric ylide, its conformation and face selectivity. We therefore embarked on the synthesis of alternative chiral sulfides but this time without being constrained to the camphor skeleton.

Novel chiral thianes and 1,4-oxathianes

In the previous section we described the use of a variety of chiral sulfide catalysts derived from camphor in the catalytic *in situ* epoxidation of aldehydes (Scheme 1). Although we achieved higher yields than we had with 1,3-oxathiane **1**, none of the new catalysts approached the high level of enantioselectivity obtained with **1**. Consequently, it seemed necessary to prepare a range of chiral sulfides derived from materials other than camphor which all incorporated the basic structural features of 1,3-oxathiane **1**. As depicted in Fig. 6, we sought conformationally locked cyclic sulfides in which the axial lone pair would be hindered by an axial substituent. In addition, ylide conformation and face selectivity needed to be controlled and we proposed to achieve this through non-bonded steric interactions. Sulfides **28**–**32** (Fig. 7) were designed to incorporate the three criteria required for high enantioselectivity as described in the introduction. In addition, sulfides **29**–**32** are conformationally locked, thus providing a rigid framework for the sulfur ylide.

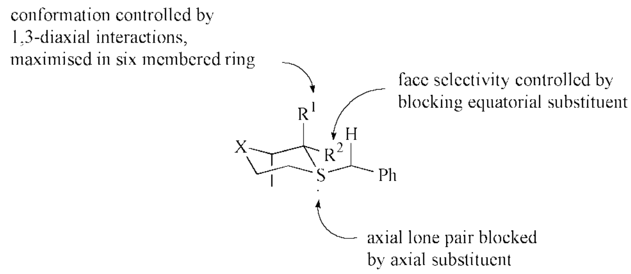


Fig. 6

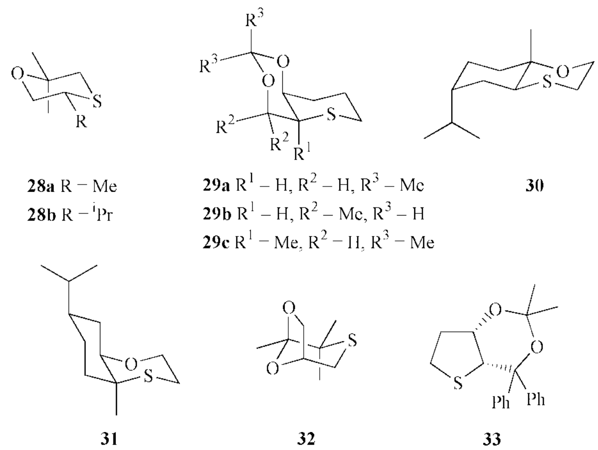
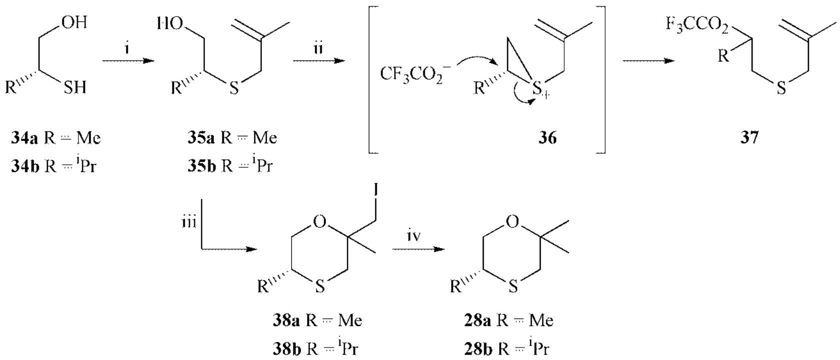


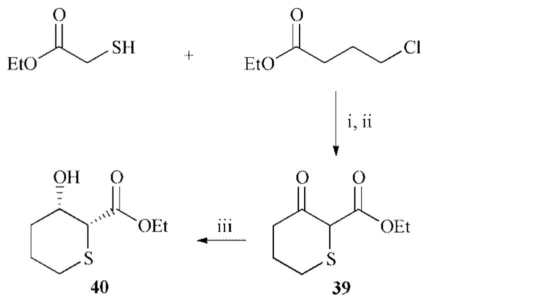
Fig. 7

The 1,4-oxathianes **28a** and **28b** were prepared as shown in Scheme 8. Alkylation of the known hydroxythiols **34a** and **34b**,[20] accessible from methyl (*S*)-lactate and L-valine respectively, with methallyl bromide provided the allylic sulfides **35a** and **35b** in good yields.[21] We had originally hoped to apply an acid-mediated cyclisation[22] of **35a** and **35b** to afford sulfides **28a** and **28b**, but with all reagents tried we obtained either decomposition or return of starting material. Alternatively, when **35a** was treated with trifluoroacetic acid, sulfide **37** was obtained in high yield, presumably *via* regioselective opening of the episulfonium ion **36**.[23] Consequently, we subjected **35a** and **35b** to iodocyclisation[24] to afford the 1,4-oxathianes **38a** and **38b** in an inconsequential 1 : 1 ratio of diastereomers. Excision of the iodine with either $LiEt_3BH$ or $LiAlH_4$ completed the synthesis of sulfides **28a** and **28b**. Subsequent chiral GC analysis of sulfides **28a** and **28b** indicated that although **28a** was prepared in 98% ee, sulfide **28b** was only 66% ee.[25] The partial racemisation of **28b** is presumed to emanate from hydroxythiol **34b**, which is reported to be prepared in only 81% ee from L-valine.[20a]

The key intermediate in the synthesis of sulfides **29a**, **29b** and **29c** was β-hydroxyester **40**, accessible from β-ketoester **39** as shown in Scheme 9. The procedure of Fehnel was used to prepare **39** in two steps,[26] which was subjected to Baker's yeast reduction, following the precedent of the enantioselective yeast reduction of the carbocyclic analogue of **39** reported by Seebach and other groups.[27–29] The desired product **40** was obtained with complete *syn* diastereoselectivity and good enantioselectivity (82% ee), which could be raised to 100% enantiopurity by crystallisation from ether–hexane (Fig. 8). The first target sulfide **29a** was prepared in two simple steps as shown in Scheme 10. Reduction of **40** with lithium aluminium hydride to afford diol **41**, followed by reaction with 2,2-dimethoxypropane and catalytic PPTS provided acetal **29a**.[30] The geminal dimethyl sulfide **29b** was obtained by reaction of methylmagnesium bromide with **40** to provide diol **42**, followed by acetalisation (Scheme 11). During the course of this work,



Scheme 8 *Reagents and conditions*: i methallyl bromide, NaOMe, MeOH, 72% (R = Me) or 64% (R = ^{i}Pr); ii TFA, CH_2Cl_2, 86% (R = Me); iii I_2, $NaHCO_3$, CCl_4, H_2O, 80% (R = Me) or I_2, Na_2CO_3, MeCN, 55% (R = ^{i}Pr); iv $LiEt_3BH$, THF, 60% (R = Me) or $LiAlH_4$, THF, 64% (R = ^{i}Pr).



Scheme 9 *Reagents and conditions*: i NaOEt, EtOH; ii NaOEt, Et_2O; iii Baker's yeast, H_2O, 66%.

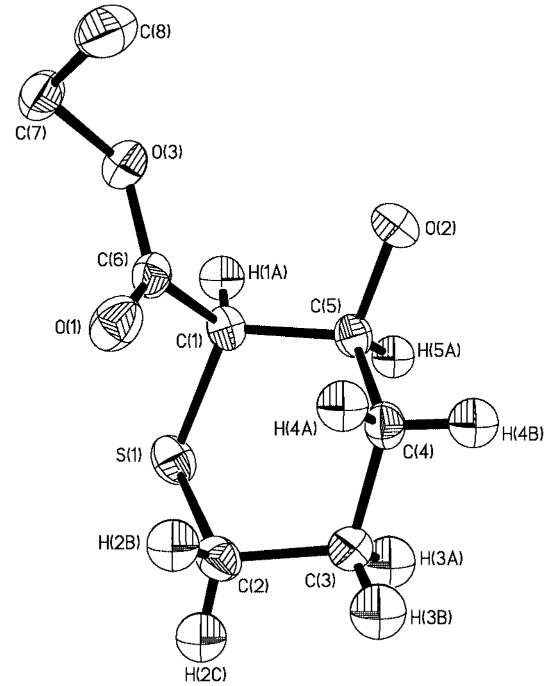
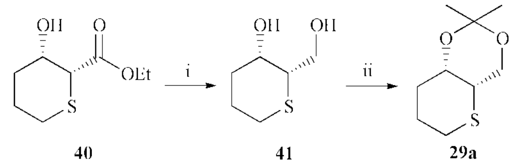
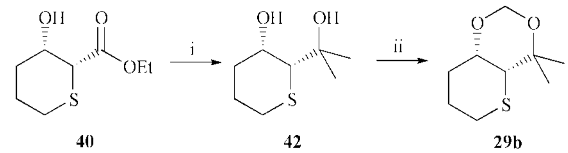


Fig. 8 ORTEP drawing of β-hydroxyester **40**.

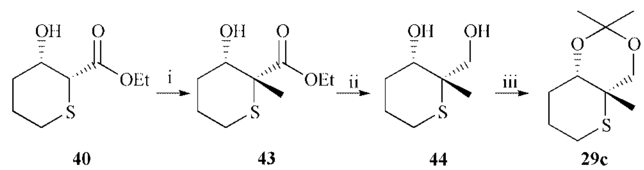
Hayakawa and Shimizu described the synthesis of a related sulfide **33** (Fig. 7) using a similar strategy, which gave 78% ee in the epoxidation of benzaldehyde using conventional conditions (BnBr, NaOH, MeCN).[6m] The preparation of α-methyl substituted **29c** was accomplished as shown in Scheme 12, utilising the procedure of Fráter for the α-alkylation of β-hydroxyesters.[31] Thus, treatment of **40** with lithium diisopropylamide at −50 °C, slow warming of the dianion to −15 °C over two hours, followed by alkylation with methyl iodide in HMPA furnished sulfide **43** in 81% yield and as an inseparable 6 : 1 mixture of diastereomers in favour of the product shown. Subsequent reduction with $LiAlH_4$ and acetalisation proceeded well to afford a diastereomeric mixture of acetals, which were separated by chromatography to provide sulfide **29c** as the major product.



Scheme 10 *Reagents and conditions*: i $LiAlH_4$, Et_2O, 76%; ii $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 86%.

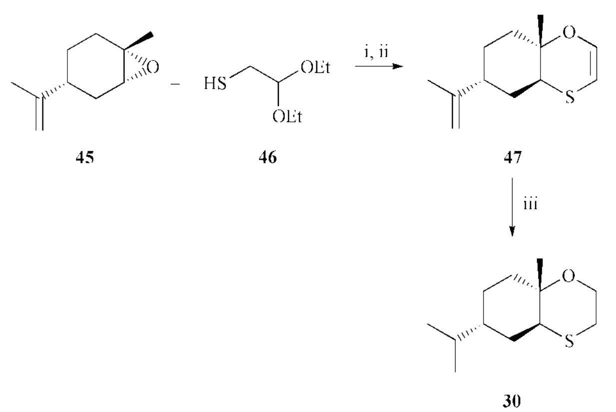


Scheme 11 *Reagents and conditions*: i MeMgBr, THF, 75%; ii $(MeO)_2CH_2$, PPTS, CH_2Cl_2, 29%.



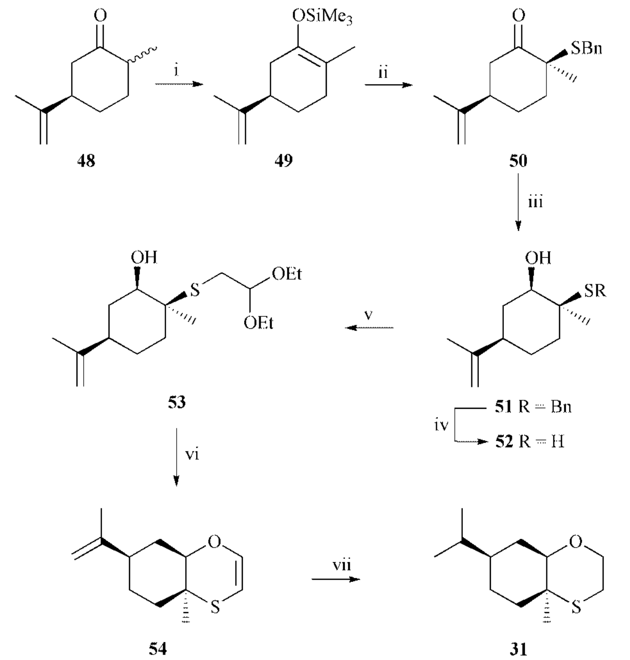
Scheme 12 *Reagents and conditions*: i LDA, THF, then MeI, HMPA, 81% (6 : 1 mixture of diastereoisomers); ii $LiAlH_4$, Et_2O, 77%; iii $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 82% (mixture of diastereoisomers).

Sulfide **30** was synthesised from *trans*-limonene oxide **45** (Scheme 13). Thus, treatment of **45** with the sodium thiolate derived from mercaptoacetaldehyde diethyl acetal **46**[32] afforded the epoxide-opened product which was immediately cyclised under the mediation of $BF_3·OEt_2$ to give unsaturated 1,4-oxathiane **47**. It was not possible to use *cis*-limonene oxide as no reaction occurred with the thiolate derived from **46**. Hydro-



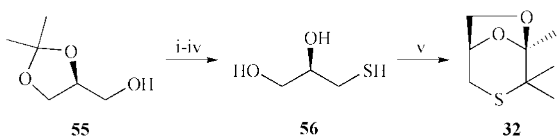
Scheme 13 *Reagents and conditions*: i NaH, DMF; ii $BF_3·OEt_2$, Et_2O, 80% over two steps; iii H_2, Pd–S/C, EtOH, 80%.

genation of **47** furnished the desired 1,4-oxathiane **30** in good yield. The synthesis of **31** proceeded from (+)-dihydrocarvone **48**, which was converted to silyl enol ether **49** using a known method as shown in Scheme 14.[33] Treatment of **49** with methyl-



Scheme 14 *Reagents and conditions*: i CH_3CN, Et_3N, TMSCl, NaI, 80 °C, ii MeLi, THF, then $BnSS(O)_2C_6H_4(CH_3)$, HMPA, THF, 82% (4 : 1 mixture of diastereomers); iii DIBAL-H, CH_2Cl_2, 67%; iv Na, NH_3, THF, used crude in next step; v $BrCH_2CH(OEt)_2$, KOH, EtOH, 39% from **51**; vi BF_3·OEt_2, Et_2O, 50%; vii H_2, Pd–S/C, EtOH, 60%.

lithium at 0 °C generated the enolate which was transferred by cannula into a solution of benzyl toluene-*p*-thiosulfonate and HMPA to give the benzyl sulfide **50** as a 4 : 1 mixture of diastereoisomers in favour of **50**, which could not be separated at this stage.[14,34–36] Reduction of ketone **50** with DIBAL-H gave the corresponding alcohol **51** in an isolated yield of 67%. Debenzylation of **51** proceeded well to provide hydroxythiol **52**, which was immediately coupled with bromoacetaldehyde diethyl acetal under basic conditions to furnish hydroxyacetal **53**.[14] Attempts to form sulfide **31** directly from **53** with boron trifluoride–diethyl ether–triethylsilane were unsuccessful, with a significant by-product being unsaturated 1,4-oxathiane **54**. Consequently, treatment of **53** with excess boron trifluoride–diethyl ether furnished **54** cleanly in moderate yield, which was hydrogenated to afford 1,4-oxathiane **31**. Sulfide **32** has been prepared previously from thiol **56** and 3-hydroxy-3-methylbutan-2-one, although only in racemic form.[37] We utilised this procedure employing enantiomerically pure thiol **56**, derived from acetonide **55** by the method of Chu,[38] to afford sulfide **32** (Scheme 15).



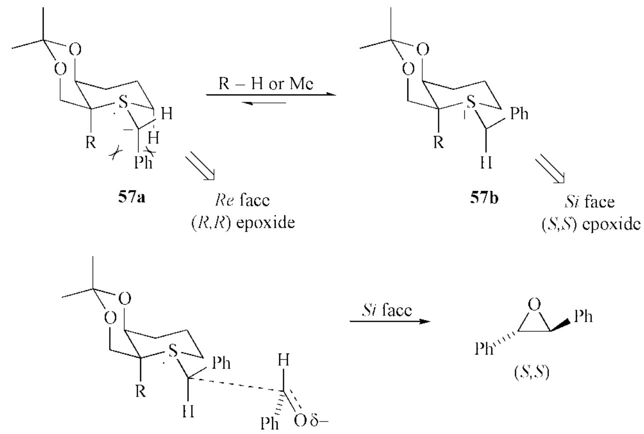
Scheme 15 *Reagents and conditions*: i TsCl, NEt_3, $CHCl_3$, 71%; ii BnSH, NaOEt, EtOH, 69%; iii Na–NH_3, 60%; iv AcOH, 58%; v 3-hydroxy-3-methylbutan-2-one, TsOH, *o*-xylene, 25%.

Results of epoxidation. Sulfides **28**–**32** were tested in the catalytic cycle with benzaldehyde, using the new *in situ* conditions (Scheme 6, Table 2). Good to excellent yields were obtained using sulfides **28a**, **28b**, **29a**, **29c** and **31** (entries 1, 2, 3, 5 and 7), whilst somewhat lower yields using **29b** and, particularly, **32** reflected the more sterically hindered nature of these sulfides (entries 4 and 8). However, the enantioselectivities observed were only moderate for sulfides **28a**, **28b**, **29a**, **29c**, **31** and **32** and low for **29b** and **30**, contrasting with those obtained with 1,3-oxathiane **1**, where concerted steric and electronic factors contribute to the high enantioselectivity. The following rationale, illustrated for related sulfides **29a** or **29c**, can be invoked to account for the asymmetric induction observed (Scheme 16).

Table 2 Yields and enantioselectivities for epoxidation

Entry	Sulfide	Yield (%)[a]	*trans* : *cis*[b]	ee (%)[c]
1	**28a**	80	95 : 5	70 (*R*,*R*)
2	**28b**	75	95 : 5	48 (*R*,*R*)[d]
3	**29a**	92	92 : 8	77 (*S*,*S*)
4	**29b**	62	90 : 10	20 (*S*,*S*)
5	**29c**	65	92 : 8	68 (*S*,*S*)
6	**30**	45	95 : 5	41 (*S*,*S*)
7	**31**	77	95 : 5	66 (*S*,*S*)
8	**32**	9	95 : 5	60 (*R*,*R*)

[a] Isolated yield. [b] By ^{1}H NMR. [c] Measured on a Chiralcel OD column. [d] Sulfide **28b** only 66% ee by chiral GC.



Scheme 16

Only the equatorial sulfur lone pair of **29a** or **29c** should be accessible, and hence only one diastereomer of the ylide should be formed upon reaction of the sulfide with the rhodium carbenoid. This ylide can adopt conformations **57a** or **57b**, but **57b** should be favoured due to 1,3-diaxial interactions in **57a**. The facial selectivity of **57b** should then dictate that the *Si* face be more accessible to benzaldehyde, leading to the formation of the (*S*,*S*)-epoxide, which was the observed major enantiomer. We were surprised that **29c** gave lower enantioselectivity than **29a** especially because both ylide conformation and face selectivity should be better controlled in **29c**. We cannot account for this observation at present.

Similar arguments can be advanced for the observed absolute stereochemistry of the *trans*-stilbene oxide obtained from sulfides **28a**, **28b**, **30**, **31**, and **32**, with the major ylide conformation and facial selectivity shown in Fig. 9. Sulfide **29b**, containing a blocking equatorial methyl group, was further evaluated. The asymmetric induction observed was considerably lower than that previously seen but can be accounted for by the following model (Scheme 17). In this case, it is possible that both sulfur lone pairs may be equally hindered: the axial lone pair by the axial oxygen and the equatorial lone pair by the equatorial methyl group. This would produce a diastereomeric mixture of sulfur ylides **58** and **59**. Conformations **58b** and **59b** should be favoured on consideration of 1,3-diaxial interactions, but the respective facial selectivity of ylides **58b** and **59b** would give rise to enantiomeric products.

We were surprised that the sulfides we had carefully designed, which we believed would largely control ylide formation, conformation and face selectivity, were still inferior to the camphor

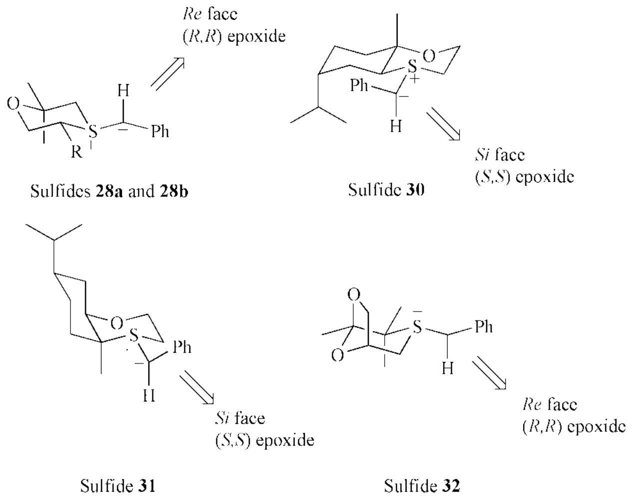
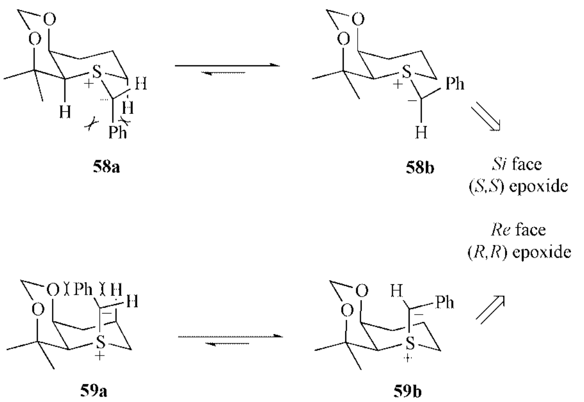


Fig. 9



Scheme 17

derived 1,3-oxathiane **1**. As we were clearly unable to control all three features that we perceived were required to achieve high enantiocontrol we decided to eliminate one of them. We decided to avoid the possibility of formation of diastereomeric mixtures of sulfur ylides by using C_2 symmetric sulfides.

C_2 symmetric chiral sulfides

C_2 symmetric sulfides have been utilised previously in stoichiometric sulfonium ylide epoxidations, notably by Durst[6b] and Metzner.[6k,6l] As shown for the generic sulfide structure in Fig. 10, ylide conformation and face selectivity should be controlled by non-bonded interactions. We therefore embarked on the synthesis and application of a variety of C_2 symmetric sulfides **60**–**65** (Fig. 11) in the new *in situ* catalytic epoxidation cycle.

Sulfides **60a**,[6l] **64**,[39] **65a**[40] and **65b**[41] were prepared as described in the literature. The synthesis of sulfide **61** was achieved as shown in Scheme 18. Following the procedure of Smith and Boldi,[42] dithiane **66** was dialkylated with (*S*)-glycidyl† methyl ether **67** to furnish diol **68** following desilylation with TBAF in 63% yield over two steps. Cleavage of the dithiane moiety in **68** with Raney nickel was slow, providing diol **69** in low yield. Subsequent mesylation and cyclisation with lithium sulfide afforded sulfide **61**.[6l] The corresponding cyclic diol **62** was prepared in a similar manner to **61**, starting from the dialkylation of sulfone **70** with (*R*)-glycidyl benzyl ether **69** (Scheme 19) reported by Najdi and Kurth,[43] which gave diol **73** in 50% yield, together with monoalkylated **72**. Desulfonylation of diol **73** with sodium–mercury amalgam, tosylation, subsequent cyclisation with lithium sulfide and debenzylation gave the required sulfide **62**. We also wished to prepare con-

† The IUPAC name for glycidyl is 2,3-epoxypropyl.

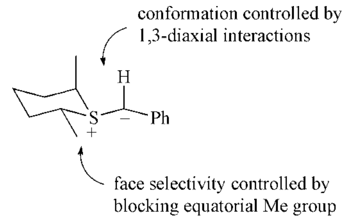


Fig. 10

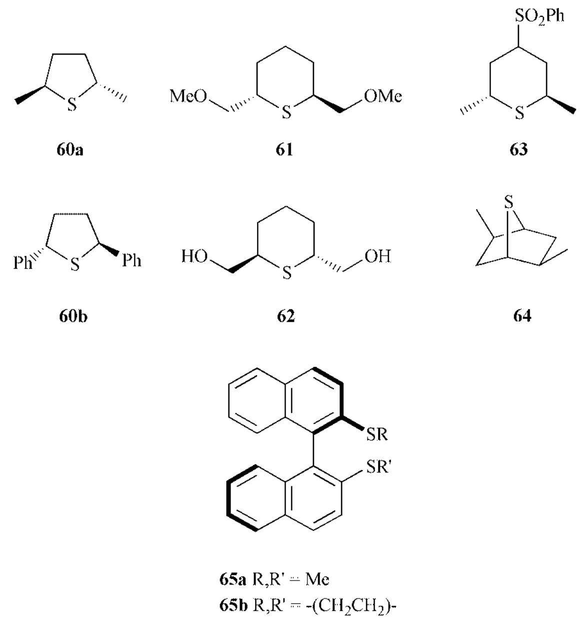
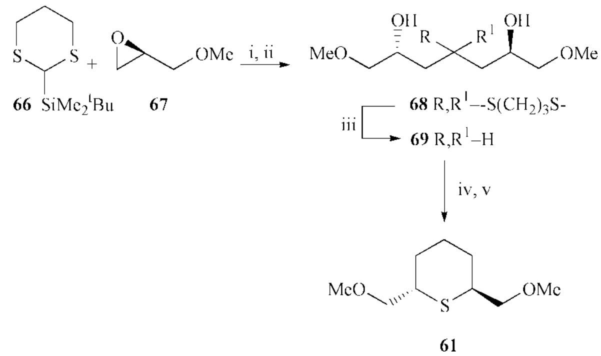


Fig. 11

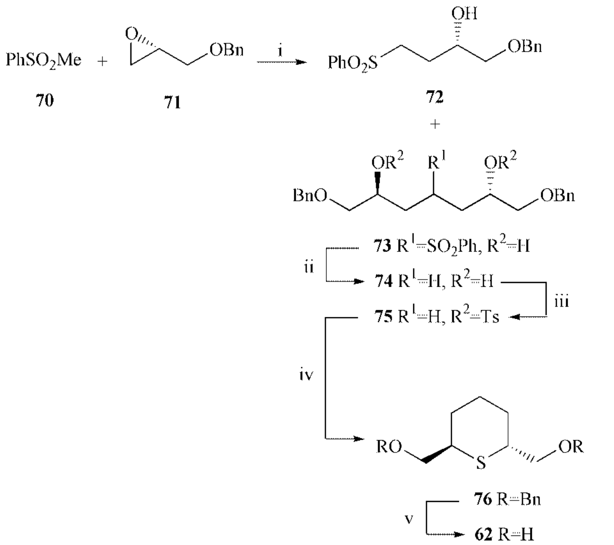


Scheme 18 *Reagents and conditions*: i ᵗBuLi, HMPA, THF, **67**; ii TBAF, THF, 63% over two steps; iii Raney Ni, EtOH, 27%; iv MsCl, pyridine, CH_2Cl_2; v Li_2S, DMSO, 43% over two steps.

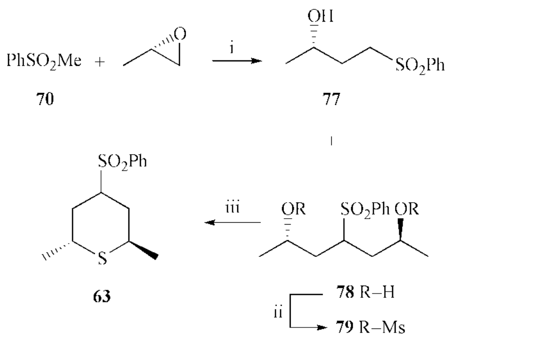
formationally locked **63** and this was accomplished as shown in Scheme 20. Dialkylation of sulfone **70** with (*S*)-propylene oxide according to the procedure of Najdi and Kurth[43] gave the required diol **78** in 58% yield, together with some monoalkylated product **77**. Subsequent mesylation of **78** and cyclisation with lithium sulfide furnished the cyclic sulfide **63**.

Results of epoxidation

Sulfides **60**–**65** were tested in the catalytic cycle with benzaldehyde, using the new *in situ* conditions (Scheme 6, Table 3). However, in general, low enantioselectivities were observed. 2,5-Dimethylthiolane **60a** gave *trans*-stilbene oxide in moderate yield and enantioselectivity (entry 1). However, this result stands in contrast to the work of Metzner and co-workers who employed a stoichiometric amount of **60a** together with benzyl bromide and benzaldehyde under basic conditions in acetonitrile–water (9 : 1) to afford *trans*-stilbene oxide in 84% ee.[6k,6l] The wide discrepancy in enantioselectivities using **60a** under the Metzner conditions and our *in situ* reaction, which



Scheme 19 *Reagents and conditions*: i *n*-BuLi, HMPA, THF, then **71**, 50% (plus 40% of **72**); ii Na–Hg, 73%; iii TsCl, Et_3N, CH_2Cl_2, 88%; iv Li_2S, DMF, 43%; v Na–NH_3, 54%.



Scheme 20 *Reagents and conditions*: i *n*-BuLi, HMPA, THF, then (*S*)-propylene oxide, 58% (plus 24% of **77**); ii MsCl, pyridine, CH_2Cl_2, 41%; iii Li_2S, DMF, 81%.

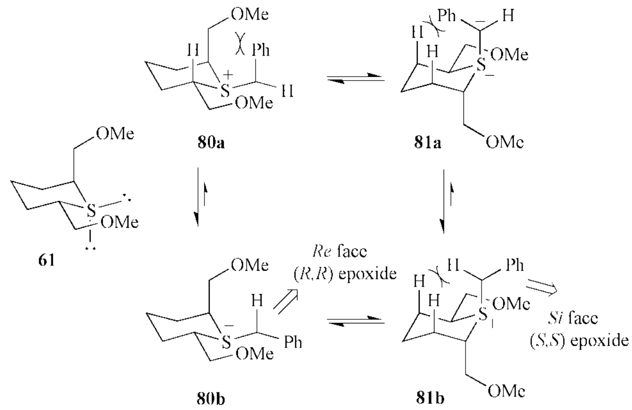
Table 3 Yields and enantioselectivities for epoxidation

Entry	Sulfide	Yield (%)[a]	*trans* : *cis*[b]	ee (%)[c]
1	**60a**	55	92 : 8	48 (*R*,*R*)
2	**60a**	40	92 : 8	87 (*R*,*R*)[d]
3	**60b**	0	—	—
4	**61**	10	95 : 5	43 (*S*,*S*)
5	**62**	41	95 : 5	8 (*S*,*S*)
6	**63**	64	98 : 2	3 (*S*,*S*)
7	**64**	73	97 : 3	18 (*S*,*S*)
8	**65a**	78	95 : 5	11 (*R*,*R*)
9	**65b**	0	—	—

[a] Isolated yield. [b] By ^{1}H NMR. [c] Measured on a Chiralcel OD column. [d] In MeCN–H_2O (9 : 1).

presumably share a common benzyl ylide species, was not easy to reconcile. However, Metzner reported a substantial dependence of the yield and enantioselectivity on the particular solvent mixture employed in his process. In order to probe whether a similar effect operated in our *in situ* reaction employing **60a** as catalyst, we conducted an *in situ* epoxidation in acetonitrile–water (9 : 1). In test reactions with tetrahydrothiophene, this solvent mixture gave superior yields compared to *tert*-BuOH–water (9 : 1), EtOH–water (9 : 1) and 1,4-dioxane–water (9 : 1). Under these new conditions, a substantially improved enantioselectivity was indeed achieved, although in lower yield (entry 2). Alternative solvents (THF, toluene, 1,4-dioxane) were investigated with **60a**, but in no case did the enantioselectivities approach those observed in acetonitrile–water, nor could yields be improved using this solvent mixture. Sulfide **60b**, which has a radical stabilising group (Ph) α to sulfur, furnished no epoxide (entry 3), perhaps because of the intervention of a facile competitive Stevens rearrangement.

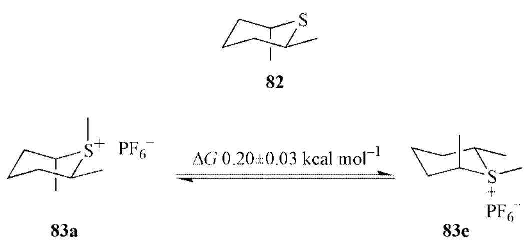
The sulfur lone pairs on **61** are equivalent through ring inversion as shown in Scheme 21. The ylide formed upon



Scheme 21

reaction of the equatorial sulfur lone pair with the rhodium carbenoid can adopt conformations **80a** or **80b**, but **80b** should be favoured due to 1,3-diaxial interactions in **80a**. Ring inversion of **80a** and **80b** leads to conformation **81a** or **81b** respectively, which is equivalent to formation of the ylide through reaction of the axial lone pair. Conformation **81b** should be favoured over **81a** due to less stringent 1,3-diaxial interactions. The conformational freedom of **61** means that a mixture of conformers **80b** and **81b** will be present. The facial selectivity of **80b** should dictate that the *Re* face be more accessible to benzaldehyde, leading to the formation of the (*R*,*R*)-epoxide. Conversely, ylide **81b** should lead to the formation of the (*S*,*S*)-epoxide. This could account for the low enantioselectivity observed with this catalyst.

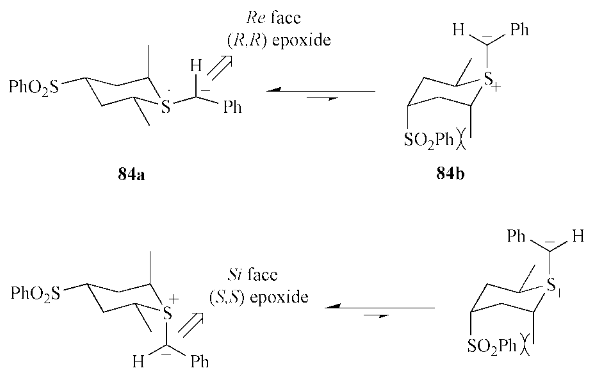
Although the axial conformer **81b** may seem to be highly disfavoured on the basis of 1,3-diaxial interactions, it needs to be considered given that Eliel and Willer have shown that the C_2 symmetric thiane **82** has a small preference for the axial *S*-methyl conformer **83a** (Scheme 22).[44] Thermal equilibration



Scheme 22

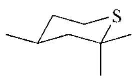
at sulfur occurred by heating at 100 °C in CD_3CN for several hours. Evidently, the two *gauche* interactions in **83e** are greater than the sum of a single *gauche* interaction with 1,3-diaxial interactions present in **83a**. Similar arguments can be advanced for sulfides **61** and **62** (entries 4 and 5).

In order to restrict the ring inversion observed for sulfides **61** and **62**, we tested the conformationally locked thiane **63** (Scheme 23). The ylide formed upon reaction of the equatorial lone pair should adopt conformation **84a**, based on similar arguments detailed above for **61**. Ring inversion to form conformer **84b** should be negligible. Similarly, ylide **85a**, formed through reaction of the axial lone pair, should be the major conformer. Ylides **84a** and **85a** have opposite facial selectivities and based on the very low enantioselectivity observed (entry 6), it seems likely that a diastereomeric mixture of ylides **84a** and **85a** was present. There is evidence in the literature which suggests that this scenario is likely. Alkylation of the conforma-

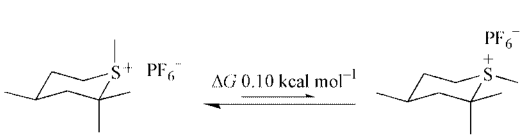


84a **84b** **85a** **85b**

Scheme 23



86

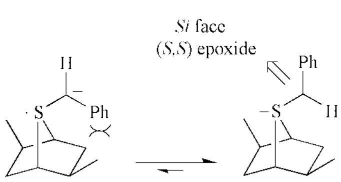


87a **87e**

Scheme 24

tionally locked thiane **86** was reported to proceed in a 65 : 35 ratio in favour of the equatorial diastereomer **87e** (Scheme 24).[44] The proposed reason for the greater than expected proportion of the axial *S*-methyl diastereomer **87a** was a large interaction between the axial 2-methyl and the equatorial *S*-methyl in **87e**, which is absent in **87a**. The interaction between the axial 2-methyl and the equatorial *S*-methyl in **87e**, which is absent in **87a** is manifested in equilibration studies (heating at 100 °C in CD_3CN for several hours), which resulted in a small preference for the axial conformer **87a**. Facile flattening of the ring at sulfur upon alkylation bends the axial 2-methyl group towards the vicinal equatorial *S*-methyl accentuating this interaction. The same arguments can be applied in ylide formation from sulfide **63** leading to a low diastereomeric ratio of **84a** : **85a**.

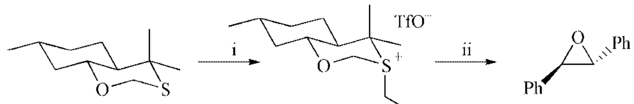
The bicyclic thiane **64** contains equivalent lone pairs and the conformation of the ylide should be controlled by non-bonded interactions between the phenyl group and thiane ring (Scheme 25). The low enantioselectivity observed (entry 7) is probably due to the methyl groups not being able to effectively block one face of the ylide. The binaphthyl group has proven to be an excellent scaffold for numerous successful asymmetric catalysts, but in the case of the binaphthyl sulfide **65a** a poor enantioselectivity was observed (entry 8).[40] This is most likely attributable to the formation of a diastereomeric mixture of ylides coupled with some conformational freedom of the ylide.



Scheme 25

Unfortunately, the less conformationally mobile sulfide **65b** was not soluble in a range of solvents and gave no epoxide (entry 9).[41]

The strategies described above have not been successful in delivering sulfides which give high yields and high enantioselectivities in epoxidation. We now believe the much higher enantioselectivity observed with 1,3-oxathiane derived ylides may be due to the anomeric effect.[5b] Indeed, Solladié-Cavallo's sulfide **88**,[6g] which is the only other sulfide that gives high enantioselectivity, is also a 1,3-oxathiane (Scheme 26). The

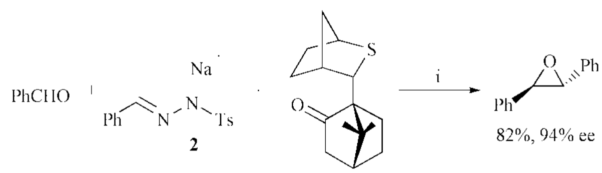


88

Scheme 26 *Reagents and conditions*: i BnOH, pyridine, Tf_2O; ii NaH, CH_2Cl_2, PhCHO, −40 °C.

oxygen of the 1,3-oxathiane will stabilise the ylide through overlap of its equatorial lone pair with the C–S σ* orbital. This stabilisation will be maximal if the oxathiane retains its chair conformation. In doing so, 1,3-diaxial interactions between the ring and substituents on the ylide carbon are maintained, leading to the formation of essentially a single ylide conformer. High face selectivity in the reactivity of the ylide then leads to high enantioselectivity in epoxidation. Without anomeric stabilisation, we now believe that flattening of the ring in the ylides derived from the thianes and 1,4-oxathianes occurs and this would lead to reduced 1,3-diaxial interactions. Such reduced interactions would result in the presence of significant amounts of both ylide conformers, leading to lower enantioselectivity. There is substantial evidence that torsional deformation of substituted thianes occurs upon alkylation resulting in flattening of the ring. This has been observed in both X-ray and NMR analysis of *S*-methylthiolanium salts.[44,45] Furthermore, Barbarella and Dembech[46] found from detailed NMR studies that thiane and substituted derivatives actually exist in half chair conformations and that upon alkylation significant deformation to quasi-envelope conformations occurred. Thus, the erosion in enantioselectivity most likely originates from facile deformation of the chair conformation of thianes leading to poor control in the conformation of the ylide. Clearly what was required were conformationally much more rigid sulfides.

This analysis led to the design and synthesis of the conformationally locked bridged bicyclic sulfide **89** (Scheme 27). This



2

89 (5 mol%)

Scheme 27 *Reagents and conditions*: i 1 mol% $Rh_2(OAc)_4$, 5 mol% $BnEt_3N^+Cl^-$, CH_3CN, 40 °C.

sulfide retained the three criteria described in the Introduction but in addition was completely rigid, and so could not undergo any subtle changes in bond angles and therefore flattening of the ring upon ylide formation. As such, ylide conformation was much better controlled. This sulfide finally led to high enantioselectivity in the epoxidation process.[7]

Conclusions

We have recently described a new method for converting carbonyl compounds into epoxides using tosylhydrazone salts and catalytic quantities of $Rh_2(OAc)_4$ and sulfide. The reaction occurs *via* the corresponding diazo compound. However, 1,3-oxathianes derived from camphorsulfonyl chloride, which previously gave high yield and high enantioselectivity when phenyldiazomethane was employed, only gave low yields in the new process. A broad range of more robust, chiral sulfides were therefore prepared based on thianes, thiolanes, 1,4-oxathianes and other bicyclic ring systems. The sulfides were largely designed based on the following criteria: (i) only one of the two lone pairs should be accessible so that a single diastereomer of the sulfur ylide was formed (this of course did not apply to the C_2 symmetric thianes/thiolanes); (ii) the conformation of the ylide should be controlled through 1,3-diaxial type interactions; (iii) the face selectivity of the ylide should be controlled by blocking substituents on the ring, making one face much more hindered than the other. The sulfides all proved to be stable to the reaction conditions and gave high yields of epoxides. Even though most sulfides conformed to the above criteria the enantioselectivity was only modest. This has been attributed to poor control in the conformation of the ylide due to the flexible nature of the sulfide as thianes and thiolanes are particularly prone to facile flattening of the ring to avoid steric repulsions. This analysis led to the design of the conformationally rigid [2.2.1] bridged bicyclic sulfide **89**, which finally led to high enantioselectivity. Note added in proof: oxathiane **7** has recently been reported and employed in related sulfur ylide reactions.[47]

Experimental

^1H and ^{13}C magnetic resonance spectra were recorded using a Bruker ACS-250 and a Bruker AMX-2 400 spectrometer supported by an Aspect 2000 data system. The ^1H chemical shifts were recorded on the δ scale and were measured relative to the residual signal of chloroform at δ 7.25. ^{13}C chemical shifts were measured from the central peak of chloroform at δ 77.0. Coupling constants are measured in hertz. Mass spectra were recorded using a Kratos instrument. Infrared spectra were obtained on a Perkin-Elmer Paragon 1000 FTIR instrument. Melting points were determined on a Gallenkamp apparatus and stand uncorrected. Elemental microanalyses were carried out using a Perkin-Elmer 2400 Elemental Analyser CHN, involving classical analysis for sulfur. Optical rotations were recorded on an Optical Activity AA-10 polarimeter at 589 nm with a path length of 1 dm and are reported in units of 10^{-1} deg $cm^2\ g^{-1}$. Concentrations (*c*) are quoted in g 100 cm^{-3}. Thin layer chromatography (TLC) was used routinely to monitor the progress of reactions and purity of compounds. TLC was performed on Merck Kieselgel 60 F_{254} aluminium backed TLC plates containing fluorescent indicator. Visualisation was achieved with 254 nm UV light and by treatment with either a solution of phosphomolybdic acid (5 g in 100 cm^3 of 95% ethanol) or 1% w/v aqueous potassium permanganate, followed by warming of the TLC plate with a heat gun. Chromatographic purification of compounds was achieved by flash chromatography using Kieselgel 60 F_{254} 40–63 micron silica gel. Reactions were generally run in oven dried glassware under nitrogen. Liquid reagents were distilled before use, while solid reagents were generally used as supplied. Solvents were dried and distilled by conventional methods.

Enantiomeric excesses were determined by chiral HPLC using a Chiralcel OD column (1% *i*-PrOH–hexane, 2 $cm^3\ min^{-1}$) for *trans*-stilbene oxide and a Chiralcel OJ column (2% *i*-PrOH–hexane, 2 $cm^3\ min^{-1}$) for β-hydroxyester **40**. The enantiomeric excesses of sulfides **28a** and **28b** were determined by chiral GC using a β-cyclodextrin column (100 °C isothermal). (Retention times: (*S*)-**28a** 6.58, (*R*)-**28a** 6.73 min and (*S*)-**28b** 15.42, (*R*)-**28b** 15.87 min.) Compounds **10**,[8] **19**,[48] **23**,[49] **34a**,[20] **34b**,[20] **39**,[26] **46**,[32] **49**,[33] **55**,[38] **56**,[38] **60a**,[6l] **64**,[39] **65a**[40] and **65b**[41] were prepared as described in the literature.

(1*R*,3*R*,6*S*,9*S*)-13,13-Dimethyl-12-oxa-8-thiatetracyclo-[7.2.1.1^{3,6}0^{1,6}]tridecane 3

To a solution of **11** (0.62 g, 2.40 mmol) in CH_2Cl_2 (5 cm^3) at 0 °C, was added dropwise $BF_3{\cdot}Et_2O$ (0.4 cm^3, 3.10 mmol). The resulting solution was stirred at 0 °C for 3.5 h then poured into saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (petroleum ether–Et_2O 70 : 30) to afford sulfide **3** (0.22 g, 40%) as a white solid, mp 47 °C; $[\alpha]_D^{22} = -128.8$ (*c* 1.7 in $CHCl_3$); ν_{max} (film)/cm^{-1} 1456, 1385, 1366, 1237, 1158, 1101 and 1076; δ_H (250 MHz; $CDCl_3$) 0.94 (3H, s, CH_3), 1.00 (3H, s, CH_3), 1.25–1.75 (8H, m), 2.01–2.24 (3H, m), 2.75 (1H, d, *J* 10.0, C*H*HS), 3.19 (1H, d, *J* 10.0, C*H*HS) and 5.60 (1H, t, *J* 2.0, SCHO); δ_C (63 MHz; $CDCl_3$) 23.5, 24.6, 24.8, 25.2, 31.4, 31.7, 32.0, 38.4, 42.9, 49.0, 51.4, 82.4 and 94.5; *m*/*z* (CI) 225 (MH^+, 80%) (Found: MH^+, 225.1304. $C_{13}H_{21}OS$ requires MH^+, 225.1313).

(1*R*,4*R*,6*S*,8*R*)-11,11-Dimethyl-4-(1-methylethyl)-3-thiatricyclo-[6.2.1.0^{1,6}]undecane 4

A mixture of alkene **14** (172 mg, 0.73 mmol) and palladium sulfide, 5% wt on carbon (1.72 g) in methanol (30 cm^3) was hydrogenated at 20 atm at RT for 22 h. The mixture was filtered through Celite, concentrated under reduced pressure and purified by flash column chromatography (petrol) to afford **4** (151 mg, 88%) as fine white needles; mp 54–56 °C; $[\alpha]_D^{18} = -136.4$ (*c* 0.60 in $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 2955, 1459 and 1384; δ_H (250 MHz; $CDCl_3$) 0.87 (3H, s, CH_3), 0.95 (3H, d, *J* 6.5, CH_3), 1.05 (3H, d, *J* 6.5, CH_3), 1.14 (3H, s, CH_3), 1.10–1.29 (2H, m, 2CH), 1.44–2.00 (9H, m, CH_2 and CH), 2.40–2.47 (1H, m, CHS), 2.48 (1H, d, *J* 14.5, C*H*HS) and 2.62 (1H, d, *J* 14.5, CH*H*S); δ_C (63 MHz; $CDCl_3$) 20.6, 21.0, 21.8, 22.1, 25.2, 27.2, 29.7, 34.9, 36.6, 38.8, 39.0, 44.9, 45.5, 46.9 and 47.6; *m*/*z* (EI) 238 (M^+, 34%) and 195 (100) (Found: M^+, 238.1758. $C_{15}H_{26}S$ requires M^+, 238.1755).

(1*S*,5*R*,7*R*)-10,10-Dimethyl-4-methylene-3-thiatricyclo-[5.2.1.0^{1,5}]decan-5-ol 6a

To a solution of thiol **16** (65 mg, 0.23 mmol) in THF (5 cm^3) at RT was added TBAF (0.5 cm^3, 0.5 mmol, 1.0 M in THF). After 2 h, water was added to the reaction mixture, which was then extracted with CH_2Cl_2 (3×). The combined extracts were washed with brine, dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 5 : 95) to afford **6a** (31 mg, 64%) as a colourless oil; $[\alpha]_D^{20} = -90.5$ (*c* 2.10 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3483, 2942, 1701 and 1627; δ_H (250 MHz; $CDCl_3$) 0.97 (3H, s, CH_3), 1.01–1.16 (1H, m), 1.27 (3H, s, CH_3), 1.50–1.83 (4H, m), 1.96–2.10 (2H, m), 2.14 (1H, br s, OH), 2.52 (1H, d, *J* 9.0, C*H*HS), 3.22 (1H, d, *J* 9.0, CH*H*S), 4.93 (1H, d, *J* 1.0, =C*H*H) and 5.12 (1H, d, *J* 1.0, =CH*H*); δ_C (63 MHz; $CDCl_3$) 22.0, 22.1, 26.9, 32.0, 32.1, 37.4, 46.3, 50.8, 61.7, 93.2, 101.4 and 151.8; *m*/*z* (EI) 210 (M^+, 30%), 108 (57), 95 (100) and 81 (27) (Found: M^+, 210.1085. $C_{12}H_{18}OS$ requires M^+, 210.1078).

(1*S*,5*R*,7*R*)-10,10-Dimethyl-4-methylene-3-thia-5-trimethylsilyloxytricyclo[5.2.1.0^{1,5}]decane 6b

A mixture of alcohol **6a** (95 mg, 0.45 mmol) and *N*-trimethylsilylimidazole (1.7 cm^3, 11.6 mmol) was heated at 100 °C for 1.5 h. After cooling, the reaction mixture was diluted with petroleum ether, washed with water, dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (petroleum ether) to afford **6b** (120 mg, 94%) as a colourless oil; $[\alpha]_D^{20} = -172.7$ (*c* 1.0 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2941, 1622, 1247 and 1082; δ_H (250 MHz; $CDCl_3$) 0.10 (9H, s, $Si(CH_3)_3$), 0.80–1.10 (1H, m), 0.94 (3H, s, CH_3), 1.20–2.05 (6H, m), 1.22 (3H, s, CH_3), 2.38 (1H, d, *J* 8.4, C*H*HS), 3.24–3.27 (1H, d, *J* 8.4, CH*H*S), 4.93 (1H, s, =C*H*H) and 5.07 (1H, s, =CH*H*); δ_C (63 MHz; $CDCl_3$) 1.7, 22.2, 22.6, 26.7, 31.1, 32.3, 39.1, 46.1, 51.0, 62.8, 94.1, 102.0 and 152.7; *m*/*z* (EI) 282 (M^+, 100%) and 267 (75) (Found: M^+, 282.1479. $C_{15}H_{26}OSSi$ requires M^+, 282.1474).

(1*S*,2*R*,7*S*,8*R*)-8,11,11-Trimethyl-3-oxa-6-thiatricyclo-[6.2.1.0^{2,7}]undecane 7

To a solution of vinyl ether **20** (600 mg, 3.1 mmol) in benzene (5 cm^3) was added AIBN (20 mg, 0.12 mmol) and thioacetic acid (0.66 cm^3, 9.3 mmol). The reaction mixture was irradiated with a sun lamp at RT for 2 h and then quenched by the addition of sodium hydroxide solution (10% w/v). The solution was extracted with ether (3×), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude thioacetate **21** (720 mg) [δ_H (250 MHz; $CDCl_3$) 0.89 (3H, s, CH_3), 0.90 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.22–1.42 (2H, m, 2CH), 1.51–1.71 (1H, m, CH), 1.89–2.03 (1H, m, CH), 2.07 (1H, d, *J* 4.9, CH), 2.30 (3H, s, $SCOCH_3$), 3.15 (2H, m, CH_2S), 3.39 (1H, s, CHO), 3.63 (1H, dt, *J* 9.8 and 6.7, C*H*HO) and 3.87 (1H, dt, *J* 9.8 and 6.1, CH*H*O)], which was used without further purification. To a solution of thioacetate **21** (700 mg, 2.59 mmol) in degassed methanol (10 cm^3) was added lithium hydroxide hydrate (140 mg, 3.4 mmol) at 0 °C and the mixture stirred for 20 min before quenching by the addition of saturated ammonium chloride solution. The mixture was diluted with ether (50 cm^3), acidified to pH 1 with a 1 M HCl solution and extracted with ether (3×). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude thiol **22** (550 mg) [δ_H (250 MHz; $CDCl_3$) 0.90 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.97 (3H, s, CH_3), 1.24–1.44 (2H, m, 2CH), 1.57 (1H, t, *J* 8.2, SH), 1.62 (1H, m, CH), 1.91–2.04 (1H, m, CH), 2.11 (1H, d, *J* 4.9, CH), 2.52 (2H, m, CH_2S), 3.41 (1H, s, CHO), 3.65 (1H, dt, *J* 9.8 and 6.7, C*H*HO) and 3.90 (1H, dt, *J* 9.8 and 5.8, CH*H*O)], which was used without further purification. To a solution of thiol **22** (550 mg, 2.41 mmol) in CH_2Cl_2 (10 cm^3) was added triethylsilane (1.15 cm^3, 7.2 mmol) and boron trifluoride–diethyl ether (0.90 cm^3, 7.2 mmol) at 0 °C. The reaction mixture was stirred at RT for 16 h, after which it was quenched by the addition of saturated ammonium chloride solution. The separated aqueous layer was extracted with CH_2Cl_2 (3×) and the combined organics were washed with brine, dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 10 : 90) to afford **7** (330 mg, 52% over three steps) as a colourless oil; $[\alpha]_D^{22}$ = −83.3 (*c* 1.08 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2953, 2885, 2712, 1479 and 1458; δ_H (250 MHz; $CDCl_3$) 0.82 (3H, s, CH_3), 0.93 (3H, s, CH_3), 1.01–1.19 (2H, m, 2CH), 1.39 (3H, s, CH_3), 1.60 (1H, dt, *J* 12.5 and 3.7, CH), 1.69–1.81 (1H, m, CH), 1.89 (1H, d, *J* 4.8, CH), 2.57–2.78 (2H, m, CH_2S), 3.07 (1H, d, *J* 7.0, CHS), 3.36 (1H, d, *J* 7.0, CHO), 3.54 (1H, ddd, *J* 10.6, 6.9 and 4.0, C*H*HO) and 3.86 (1H, ddd, *J* 10.6, 8.8 and 8.4, CH*H*O); δ_C (63 MHz; $CDCl_3$) 12.2, 21.4, 21.7, 24.2, 26.0, 37.6, 48.0, 48.9, 51.0, 55.9, 62.5 and 80.9; *m*/*z* (CI) 213 ([M + H]$^+$, 100%) and 102 (60) (Found: M^+, 212.1239. $C_{12}H_{20}OS$ requires M^+, 212.1234).

(1*R*,8*S*)-1,11,11-Trimethyl-3-thiatricyclo[6.2.1.0^{2,7}]undec-2(7)-ene 8

To a solution of a 7 : 3 *exo*–*endo* mixture of allylcamphor **23** (440 mg, 2.3 mmol) in benzene (15 cm^3) was added AIBN (20 mg, 0.12 mmol) and thioacetic acid (0.65 cm^3, 9.2 mmol). The reaction mixture was heated at reflux for 1 h and then quenched by the addition of sodium hydroxide solution (10% w/v). The solution was extracted with ether (3×), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude thioacetate **24**, which was immediately dissolved in degassed methanol (10 cm^3). At 0 °C, lithium hydroxide hydrate (210 mg, 4.6 mmol) was added and the mixture stirred for 20 min before quenching by the addition of saturated ammonium chloride solution. The mixture was diluted with ether (50 cm^3), acidified to pH 1 with a 1 M HCl solution and extracted with ether (3×). The combined organics extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude thiol **25**, which was immediately dissolved in CH_2Cl_2 (10 cm^3). To this solution was added boron trifluoride–diethyl ether (0.9 cm^3, 7.2 mmol) at 0 °C. The reaction mixture was stirred at RT for 16 h, after which it was quenched by the addition of saturated ammonium chloride solution. The separated aqueous layer was extracted with CH_2Cl_2 (3×) and the combined extracts were washed with brine, dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (petroleum ether) to afford **8** (300 mg, 63% over three steps) as a clear oil; $[\alpha]_D^{22}$ = −104.0 (*c* 0.90 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2983, 2949, 2869, 1619 and 1473; δ_H (250 MHz; $CDCl_3$) 0.77 (3H, s, CH_3), 0.83 (3H, s, CH_3), 0.94 (3H, s, CH_3), 0.98–1.04 (1H, m, CH), 1.12–1.22 (1H, m, CH), 1.47–1.58 (1H, m, CH), 1.75–2.00 (4H, m, 4CH), 2.05–2.14 (2H, m, CH_2) and 2.72–2.80 (2H, m, CH_2S); δ_C (63 MHz; $CDCl_3$) 10.9, 19.2, 19.3, 23.6, 25.9, 27.1, 33.2, 54.5, 55.9, 56.4, 132.7 and 133.7; *m*/*z* (CI) 209 ([M + H]$^+$, 100%), 208 (M^+, 85), 193 (30), 180 (32) and 113 (25) (Found: M^+, 208.1284. $C_{13}H_{20}S$ requires M^+, 208.1285).

7,7-Dimethyl-1-mercaptomethyl-5′-methoxyspiro[bicyclo[2.2.1]-heptane-2,2′-oxolane] 11

Cerium chloride heptahydrate (9.3 g, 25 mmol) was finely ground and heated under reduced pressure (0.5 mmHg) at 140 °C for 2 h. While the flask was still hot, argon gas was introduced. The flask was then cooled in an ice bath and THF (80 cm^3) was introduced. The resulting suspension was submitted to sonication for 1 h at RT before being cooled at −78 °C. 3,3-Dimethoxypropylmagnesium bromide[10] (25 mmol) was added dropwise to the cooled mixture. After stirring for 1 h at −78 °C the ketone **10** (1.53 g, 8.3 mmol) in THF (10 cm^3) was added dropwise and the reaction mixture was allowed to warm to RT overnight. The reaction was quenched with brine and the aqueous layer was acidified with 2 M HCl until complete dissolution of the salts and then extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. Purification of the residue by flash column chromatography (petroleum ether–Et_2O 50 : 50) gave **11** (1.7 g, 80%, 70 : 30 mixture of diastereoisomers) as a pale yellow oil; ν_{max} (film)/cm^{-1} 2984, 2936, 2827, 2562, 1482, 1463 and 1440; δ_H (250 MHz; $CDCl_3$) 0.91 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.32 (1H, d, *J* 13.0, SH), 1.58–1.90 (8H, m), 2.02 (1H, dt, *J* 3.0 and 12.0), 2.40 (1H, dd, *J* 10.0 and 14.0, C*H*HS), 2.71–2.84 (1H, m), 3.01 (1H, dd, *J* 8.0 and 14.0, C*H*HS), 3.35 (3H, s, OCH_3) and 4.94–4.96 (1H, m, OCHO); δ_C (63 MHz; $CDCl_3$) 20.7, 21.1, 22.6, 26.4, 27.8, 31.7, 34.6, 45.9, 48.9, 50.4, 53.9, 54.4, 93.6 and 104.7.

(1*S*,2*R*,4*R*)-1-Mercaptomethyl-7,7-dimethyl-2-(3,3-dimethyl-prop-2-enyl)bicyclo[2.2.1]heptan-2-ol 12

A mixture of lithium (230 mg, 32.6 mmol) and naphthalene (4.18 g, 32.6 mmol) in THF (40 cm^3) was stirred at RT for 4 h, after which 3,3-dimethylprop-2-enyl phenyl sulfide (2.9 g, 16.3 mmol) was added at 0 °C. The resulting red solution was stirred at 0 °C for 1 h and then added to a mixture of cerium trichloride (6.08 g, 16.3 mmol) [prepared by drying cerium trichloride heptahydrate (6.08 g, 16.3 mmol) under reduced pressure (0.5 mmHg) at 150 °C for 2.5 h before suspending in THF (50 cm^3) and sonicating for 1 h followed by stirring at RT for 1 h] at −78 °C. The resulting brown solution was stirred at −78 °C for 1 h and then ketone **10** (1.0 g, 5.43 mmol) was added portionwise over 10 min. The reaction mixture was stirred at RT for 16 h, after which it was quenched by the addition of HCl solution (2 M). The separated aqueous layer was extracted with petroleum ether (3×) and the combined extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 3 : 97) to afford **12** (790 mg, 50%) as a colourless oil together with ketone **10** (50%); ν_{max} (film)/cm^{-1} 3535, 2930 and 1667; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.26–1.36 (1H, dd, *J* 8.9 and 7.0), 1.36–2.20 (9H, m), 1.69 (3H, s, CH_3), 1.77 (3H, s, CH_3), 2.59 (1H, dd, *J* 13.4 and 7.0), 3.01 (1H, dd, *J* 13.4 and 8.9), 3.12 (1H, dd, *J* 13.4 and 9.8) and 5.15–5.45 (1H, m); δ_C (63 MHz; $CDCl_3$) 18.5, 21.4, 21.5, 23.0, 26.2, 26.7, 26.9, 39.3, 45.7, 46.8, 50.7, 55.0, 80.1, 119.6 and 137.8.

(1*S*,4*S*,6*R*,8*R*)-11,11-Dimethyl-4-(1-methylethyl)-3-thiatricyclo-[6.2.1.0^{1,6}]undecan-6-ol 13

A mixture of thiol **12** (460 mg, 1.8 mmol) and AIBN (30 mg, 0.18 mmol) in benzene (17 cm^3) was heated at reflux for 24 h. The solution was concentrated under reduced pressure and the residue purified by flash column chromatography (ethyl acetate–petrol 10 : 90) to afford **13** (257 mg, 56%) as a colourless oil; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, s, CH_3), 1.10 (3H, s, CH_3), 0.80–2.20 (18H, m), 3.15 (1H, br s) and 3.22 (1H, br s); δ_C (63 MHz; $CDCl_3$) 19.9, 20.1, 21.2, 22.6, 26.6, 27.5, 30.7, 32.6, 38.9, 44.3, 45.6, 47.1, 48.3, 50.9 and 78.5.

(1*S*,4*S*,8*R*)-11,11-Dimethyl-4-(1-methylethyl)-3-thiatricyclo-[6.2.1.0^{1,6}]undec-5-ene 14

A solution of oxalyl chloride (0.45 cm^3, 5.25 mmol) and sulfide **13** (257 mg, 1.01 mmol) in benzene (3 cm^3) was stirred at RT for 5 h, after which it was concentrated under reduced pressure and the residue purified by flash column chromatography (ethyl acetate–petrol 10 : 90) to afford **14** (193 mg, 81%) as a colourless oil; $[\alpha]_D^{20}$ = −36.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2955, 2872, 1686 and 1387; δ_H (250 MHz; $CDCl_3$) 0.76 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.98 (3H, d, *J* 7.5, CH_3), 1.01 (3H, d, *J* 7.5, CH_3), 1.13–1.29 (2H, m), 1.50–1.96 (6H, m), 2.40 (1H, d, *J* 12.8, C*H*HS), 2.76 (1H, d, *J* 12.8, CH*H*S), 3.30–3.40 (1H, m) and 5.30–5.33 (1H, m); δ_C (63 MHz; $CDCl_3$) 18.5, 19.0, 19.6, 19.7, 27.4, 28.7, 32.5, 32.9, 36.4, 44.1, 46.6, 47.7, 49.5, 118.1 and 147.2.

(1*R*,4*R*,6*S*,8*R*)-11,11-Dimethyl-4-(1-methylethyl)-3λ^4-thiatricyclo[6.2.1.0^{1,6}]undecan-3-one 15

To a solution of sulfide **4** (51 mg, 0.21 mmol) in CH_2Cl_2 (0.5 cm^3) at 0 °C was added a solution of MCPBA (44 mg, 0.26 mmol) in CH_2Cl_2. After 1 h the mixture was diluted with CH_2Cl_2 (10 cm^3) and washed with sodium bicarbonate solution (10 cm^3) and brine (10 cm^3). The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure to afford **15** (50 mg, 92%) as a crude solid which was recrystallised (ether–hexane) to obtain X-ray quality crystals; δ_H (250 MHz; $CDCl_3$) 0.78–2.14 (9H, m, 9CH), 0.87 (3H, s, CH_3), 1.04 (6H, d, *J* 4.0, $2CH_3$), 1.06 (3H, s, CH_3), 2.23 (1H, sextet, *J* 6.5, CH), 2.49–2.58 (2H, m, 2CH), 2.80 (1H, d, *J* 13.0, C*H*H) and 2.91 (1H, d, *J* 13.0, CH*H*); δ_C (63 MHz; $CDCl_3$) 18.1, 20.5, 20.6, 20.7, 27.3, 27.4, 27.7, 36.7, 38.4, 39.0, 44.6, 46.7, 48.3, 48.8 and 68.4.

Crystal structure of 15. Crystal data for $C_{15}H_{26}OS$; M = 254.42. Crystallises from *n*-hexane as colourless blocks; crystal dimensions 0.14 × 0.14 × 0.10 mm^3. Orthorhombic, a = 7.5509(7), b = 7.9475(8), c = 23.423(2) Å, U = 1405.6(2) Å^3, Z = 4, D_c = 1.202 Mg m^{-3}, space group $P2_12_12_1$ (D_2^4, no. 19), Mo-Kα radiation (λ = 0.71073 Å), μ(Mo-Kα) = 0.214 mm^{-1}, F(000) = 560. CCDC reference number 168552. See http://www.rsc.org/suppdata/p1/b1/b105416n/ for crystallographic files in .cif or other electronic format.

(1*S*,2*S*,4*R*)-1-Mercaptomethyl-7,7-dimethyl-2-(trimethylsilanylethynyl)bicyclo[2.2.1]heptan-2-ol 16

Trimethylsilylacetylene (0.15 cm^3, 1.1 mmol) was added dropwise to a solution of *n*-butyllithium (0.32 cm^3, 0.8 mmol, 2.5 M in hexanes) at −78 °C in THF (0.5 cm^3). After 30 min a solution of ketone **10** (50 mg, 0.27 mmol) in THF (0.5 cm^3) was added to the reaction mixture which was then stirred for 3 h at −78 °C. The reaction was quenched by the addition of brine and the separated aqueous layer extracted with ethyl acetate (3×). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford **16** (65 mg, 84%) as a colourless oil; $[\alpha]_D^{20}$ = +9.3 (*c* 2.68 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3462, 2956, 2161 and 842; δ_H (250 MHz; $CDCl_3$) 0.08–0.21 (9H, m, $Si(CH_3)_3$), 0.77–1.29 (3H, m), 0.90 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.49–1.83 (4H, m), 2.12–2.42 (2H, m), 2.53 (1H, dd, *J* 13.0 and 7.5, C*H*HS) and 3.01 (1H, dd, *J* 13.0 and 7.0, CH*H*S); δ_C (63 MHz; $CDCl_3$) −0.2, 20.8, 21.6, 23.4, 26.5, 29.4, 45.8, 49.5, 49.7, 56.3, 89.9, 111.3 and quaternary not visible; *m*/*z* (EI) 282 (M^+, 46%), 233 (27), 108 (52) and 73 (100) (Found: M^+, 282.1472. $C_{15}H_{26}OSSi$ requires M^+, 282.1474).

(1*R*,3*R*,4*S*)-3-(Ethenyloxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 20

To a solution of phenanthroline (100 mg, 0.56 mmol) in CH_2Cl_2 (20 cm^3) was added palladium acetate (120 mg, 0.54 mmol). The mixture was stirred at RT for 20 min after which *exo*-hydroxy camphor **19** (1.8 g, 10.71 mmol) and ethyl vinyl ether (100 cm^3) were added. Following stirring for 6 days at RT the solution was concentrated under reduced pressure and the residue purified by flash column chromatography (ethyl acetate–petrol 10 : 90) to afford **20** (820 mg, 40%) as a colourless oil and alcohol **19** (1.0 g, 55%); δ_H (250 MHz; $CDCl_3$) 0.93 (6H, s, CH_3), 0.95 (3H, s, CH_3), 1.32–1.52 (2H, m, 2CH), 1.63–1.73 (1H, m, CH), 2.02–2.08 (1H, m, CH), 2.21 (1H, d, *J* 4.8, CH), 3.81 (1H, s, CHO), 4.05 (1H, dd, *J* 14.0 and 6.6, =CH), 4.25 (1H, dd, *J* 14.0 and 2.0, =CH) and 6.50 (1H, dd, *J* 14.0 and 6.6, =CHO).

(5*R*)-2,2,5-Trimethyl-1,4-oxathiane 28a

To a solution of sulfide **38a** (1.65 g, 6.06 mmol) in THF (24 cm^3) at 0 °C was added dropwise lithium triethylborohydride (24 cm^3, 24 mmol, 1 M solution in THF). The solution was stirred at 30 °C for 24 h after which it was then poured portionwise into cold 2 M HCl. The aqueous layer was extracted with ether (3 × 50 cm^3). The combined organic extracts were washed with saturated sodium bicarbonate solution (50 cm^3) and brine (50 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ether–petrol 10 : 90) to afford **28a** (530 mg, 60%) as a yellow oil; $[\alpha]_D^{22}$ = +3.6 (*c* 0.55 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2975, 2928, 2869, 1453, 1381 and 1364; δ_H (250 MHz; $CDCl_3$) 1.13 (3H, d, *J* 7.0, CH_3CH), 1.39 (3H, s, CH_3C), 1.48 (3H, s, CH_3C), 2.40 (1H, d, *J* 13.0, C*H*HS), 2.80–3.00 (2H, m, CHS and C*H*HS), 3.57 (1H, dd, *J* 12.0 and 10.0, C*H*HO) and 3.92 (1H, dd, *J* 12.0 and 3.0, C*H*HO); δ_C (63 MHz; $CDCl_3$) 16.4, 22.1, 29.2, 34.1, 37.4, 68.5 and 69.1; *m*/*z* (CI) 147 (M^+, 100%), 88 (34), 71 (15), 63 (31) and 58 (28) (Found: $[M + H]^+$, 147.0846. $C_7H_{15}OS$ requires $[M + H]^+$, 147.0844).

(5*R*)-2,2-Dimethyl-5-(1-methylethyl)-1,4-oxathiane 28b

To a cooled (0 °C) solution of lithium aluminium hydride (380 mg, 10 mmol) in THF (25 cm^3) was added dropwise a solution of sulfide **38b** (2.0 g, 6.7 mmol) in THF (5 cm^3). At the end of the addition, the ice bath was removed and the mixture was stirred for 15 h. The mixture was then cooled to 0 °C and dilute HCl solution was added. The aqueous layer was extracted with ether (3 × 25 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ether–petrol 2 : 98) to afford **28b** (0.67 g, 64% based on recovered starting material) as a yellow oil; ν_{max} (film)/cm^{-1} 3005, 2963, 2930, 2873, 1464 and 1371; δ_H (250 MHz; $CDCl_3$) 0.96 (3H, d, *J* 6.0, CH_3CH), 0.98 (3H, d, *J* 6.0, CH_3CH), 1.25 (3H, s, CH_3C), 1.35 (3H, s, CH_3C), 1.67–1.80 (1H, m, CH_3CH), 2.35 (1H, d, *J* 13.0, C*H*HS), 2.55 (1H, ddd, *J* 10.0, 6.0 and 3.0, CHS), 2.71 (1H, d, *J* 13.0, C*H*HS), 3.71 (1H, dd, *J* 12.0 and

10.0, C*H*HO) and 3.86 (1H, dd, *J* 12.0 and 3.0, C*H*HO); δ_C (63 MHz; $CDCl_3$) 20.1, 20.2, 22.1, 29.2, 29.4, 37.5, 46.7, 65.5 and 69.4; *m*/*z* (EI) 174 (M^+, 57%), 149 (17), 116 (49), 101 (18), 69 (100), 59 (35) and 55 (55) (Found: M^+, 174.1070. $C_9H_{18}OS$ requires M^+, 174.1078).

(4a*S*,8a*S*)-2,2-Dimethylperhydrothiopyrano[3,2-*d*][1,3]dioxine 29a

To a solution of diol **41** (260 mg, 1.76 mmol) in CH_2Cl_2 (4.4 cm^3) at RT was added 2,2-dimethoxypropane (0.86 cm^3, 7.03 mmol) and PPTS (44 mg, 0.18 mmol). The mixture was stirred for 48 h, after which time it was diluted with CH_2Cl_2 (10 cm^3), washed with saturated sodium bicarbonate solution (5 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 10 : 90) to afford **29a** (285 mg, 86%) as a white solid, mp 76–78 °C; $[\alpha]_D^{23}$ = −76.9 (*c* 0.52 in $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 2923–2853; δ_H (250 MHz; $CDCl_3$) 1.40 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.51 (1H, m, C*H*H), 1.57–1.68 (1H, m, CH*H*), 1.82–1.95 (2H, m, CH_2), 2.45–2.56 (1H, m, C*H*HS), 2.66 (1H, m, CH*H*S), 2.87 (1H, br s, CH), 3.60 (1H, dd, *J* 13.0 and 1.0, C*H*HO), 4.07–4.13 (1H, m, CHS) and 4.17 (1H, dd, *J* 13.0 and 3.0, CH*H*O); δ_C (63 MHz; $CDCl_3$) 19.3, 20.2, 28.3, 29.6, 31.5, 39.1, 63.9, 64.1 and 98.9; *m*/*z* (EI) 188 (M^+, 65%) and 130 (100) (Found: M^+, 188.0872. $C_9H_{16}O_2S$ requires M^+, 188.0871).

(4a*R*,8a*S*)-4,4-Dimethylperhydrothiopyrano[3,2-*d*][1,3]dioxine 29b

To a solution of diol **42** (261 mg, 1.52 mmol) in CH_2Cl_2 (5 cm^3) at RT was added dimethoxymethane (0.5 cm^3, 5.6 mmol) and PPTS (43 mg, 0.17 mmol). The mixture was stirred at RT for 48 h, after which further dimethoxymethane (0.5 cm^3, 5.6 mmol) was added. Following stirring for a further 48 h, dimethoxymethane (0.5 cm^3, 5.6 mmol) was added and the mixture stirred for another 48 h. The reaction mixture was washed with saturated sodium bicarbonate solution (5 cm^3) and brine (10 cm^3). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 cm^3) and the combined organic extracts dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (CH_2Cl_2) to afford **29b** (84 mg, 29%) as fine white needles; $[\alpha]_D^{20}$ = −67.1 (*c* 1.44 in CH_2Cl_2); ν_{max} (Nujol)/cm^{-1} 2924, 2853 and 1377; δ_H (250 MHz; $CDCl_3$) 1.27 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.41–1.54 (1H, m, CH), 1.62–1.74 (1H, m, CH), 1.83–2.02 (1H, m, CH), 2.04–2.16 (1H, m, CH), 2.55–2.65 (2H, m, CH_2), 2.80 (1H, s, CHS), 4.10–4.18 (1H, br m, CHO) and 5.0 (2H, s, CH_2); δ_C (63 MHz; $CDCl_3$) 20.4, 22.8, 27.7, 28.0, 31.7, 47.7, 68.4, 73.8 and 88.2; *m*/*z* (EI) 188 (M^+, 39%) and 100 (100) (Found: M^+, 188.0870. $C_9H_{16}O_2S$ requires M^+, 188.0710).

(4a*S*,8a*S*)-2,2,4a-Trimethylperhydrothiopyrano[3,2-*d*][1,3]-dioxine 29c

To a solution of diol **44** (675 mg, 4.17 mmol) in CH_2Cl_2 (10 cm^3) at RT was added 2,2-dimethoxypropane (2.5 cm^3, 20.8 mmol) and PPTS (157 mg, 63 mmol). The mixture was stirred for 72 h, after which time the reaction mixture was diluted with CH_2Cl_2 (15 cm^3), washed with saturated sodium bicarbonate solution (10 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 5 : 95) to afford **29c** (305 mg, 36%) as a clear glassy solid, together with 344 mg of a mixture of **29c** and the minor diastereomer and 38 mg of pure minor diastereomer; $[\alpha]_D^{23}$ = −8.3 (*c* 0.72 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2923–2853; δ_H (250 MHz; $CDCl_3$) 1.27 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.61–1.81 (3H, m, CH_2 and C*H*H), 1.86–2.08 (1H, m, CH*H*), 2.49 (1H, td, C*H*HS), 2.83 (1H, dt, *J* 13.0 and 2.4, CH*H*S), 3.41 (1H, d, *J* 12.5, C*H*HO) and 3.72–3.77 (2H, m, CH*H*O and CH); δ_C (63 MHz; $CDCl_3$) 19.0, 20.0, 22.2, 25.4, 27.1, 29.5, 40.8, 69.3, 69.6 and 98.6; *m*/*z* (EI) 202 (M^+, 24%), 144 (53), 101 (100), 74 (91) (Found: M^+, 202.1026. $C_{10}H_{18}O_2S$ requires M^+, 202.1028).

(4a*S*,6*R*,8a*S*)-8a-Methyl-6-(1-methylethyl)perhydro-1,4-benz-oxathiine 30

To a mixture of sodium hydride (160 mg, 4.0 mmol, 60% dispersion in oil) in DMF (7 cm^3) at 0 °C was added mercapto-acetaldehyde diethyl acetal **46** (550 mg, 3.67 mmol). (1*R*,4*S*)-*trans*-Limonene oxide **45** (0.4 cm^3, 2.4 mmol) was added to the mixture which was then stirred at RT for 18 h. Hydrochloric acid solution (5 cm^3, 2 M) was added to the solution and the separated aqueous layer was extracted with ether (3 × 20 cm^3). The combined organic extracts were washed with sodium hydroxide solution (10 cm^3, 10% w/v) and brine (10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was immediately dissolved in ether (30 cm^3) and at 0 °C boron trifluoride–diethyl ether (0.9 cm^3, 7.2 mmol) was added. After stirring at RT for 3 h, the mixture was quenched by the addition of saturated ammonium chloride solution (10 cm^3) and the separated aqueous layer was extracted with ether (3 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 5 : 95) to afford **47** (410 mg, 80% over two steps) as a colourless oil [δ_H (250 MHz; $CDCl_3$) 1.32 (3H, s, CH_3), 1.32–1.64 (3H, m, 3CH), 1.70–1.77 (4H, m, CH_3 and CH), 2.07–2.15 (2H, m, 2CH), 2.38 (1H, m, CH), 3.15 (1H, dd, *J* 13.3 and 3.5, CHS), 4.86–4.98 (3H, m, vinyl CH_2 and =CHS) and 6.42 (1H, d, *J* 6.5, =CHO); *m*/*z* (EI) 210 (M^+, 100%) (Found: M^+, 210.1078. $C_{12}H_{18}OS$ requires M^+, 210.1078)]. Diene **47** was dissolved in ethanol (50 cm^3) and palladium sulfide, 5% wt on carbon (100 mg) was added. The mixture was hydrogenated (H_2 balloon pressure) at RT for 18 h, then filtered through Celite, concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 5 : 95) to afford **30** (330 mg, 80%) as a colourless oil; $[\alpha]_D^{22}$ = +3.6 (*c* 0.55 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2936, 2868, 1459, 1370 and 1298; δ_H (250 MHz; $CDCl_3$) 0.89 (6H, d, *J* 6.6, $(CH_3)_2$), 1.16–1.94 (11H, m, CH and CH_3), 2.35 (1H, dt, *J* 13.4 and 2.0, CHS), 3.02–3.07 (2H, m, CH_2S), 3.78–3.82 (1H, m, CHO) and 4.01 (1H, dt, *J* 12.3 and 2.3, CHO); δ_C (63 MHz; $CDCl_3$) 14.7, 21.3, 21.5, 25.2, 26.2, 30.3, 31.1, 34.7, 40.9, 44.9, 61.2 and 74.8; *m*/*z* (CI) 215 ([M + H]$^+$, 100%), 143 (99), 136 (35) and 129 (45) (Found: M^+, 214.1391. $C_{12}H_{22}OS$ requires M^+, 214.1387).

(4a*S*,7*R*,8a*R*)-4a-Methyl-7-(1-methylethyl)perhydro-1,4-benz-oxathiine 31

A mixture of sulfide **54** (62 mg, 0.30 mmol) and palladium sulfide, 5% wt on carbon (124 mg) in methanol (4 cm^3) was hydrogenated at 20 atm at RT for 24 h. The mixture was filtered through Celite, concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 1 : 99) to afford **31** (38 mg, 60%) as a colourless oil; $[\alpha]_D^{18}$ = +14.3 (*c* 0.14 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2955, 2871, 1451 and 1369; δ_H (250 MHz; $CDCl_3$) 0.90 (3H, d, *J* 1.5, CH_3), 0.93 (3H, d, *J* 1.5, CH_3), 1.12–1.57 (9H, m, CH_3, CH_2 and CH), 1.66–1.71 (1H, m, CH), 2.32 (1H, d, *J* 12.0, CH), 2.41 (1H, d, *J* 12.0, CH), 3.12–3.24 (1H, m, CH), 3.46 (1H, dd, *J* 12.0 and 4.0, CH), 3.70–3.77 (1H, m, CH) and 3.92 (1H, dt, *J* 12.0 and 2.5, CH); δ_C (63 MHz; $CDCl_3$) 19.9, 20.0, 24.8, 24.9, 28.4, 28.5, 32.5, 39.1, 42.3, 43.8, 58.8 and 79.3; *m*/*z* (EI) 214 (M^+, 43%), 58 (100) (Found: M^+, 214.1397. $C_{12}H_{22}OS$ requires M^+, 214.1391).

(1*R*,5*R*)-4,4,5-Trimethyl-6,8-dioxa-3-thiabicyclo[3.2.1]octane 32

To a mixture of thiol **56** (350 mg, 3.3 mmol) and PTSA (35 mg, 0.18 mmol) in *o*-xylene (15 cm^3) heated at reflux with a Dean–

Stark trap was added 3-hydroxy-3-methylbutan-2-one (0.35 cm^3, 3.3 mmol). The mixture was refluxed for 5 h, after which time, at 20 °C, sodium carbonate (150 mg) was added and the mixture stirred for a further 1 h. The solution was filtered, concentrated under reduced pressure and purified by flash column chromatography (CH_2Cl_2) to afford **32** (130 mg, 25%) as a white solid, mp 128–129 °C; $[\alpha]_D^{25} = -94.1$ (*c* 1.02 in $CHCl_3$) (Found: C, 55.2; H, 8.3; S, 18.2. $C_8H_{14}O_2S$ requires C, 55.2; H, 8.1; S, 18.4%); δ_H (250 MHz; $CDCl_3$) 1.20 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.55 (3H, s, CH_3), 2.22 (1H, dd, *J* 13.5 and 2.5, C*H*HS), 3.33–3.40 (1H, m, CH*H*S), 3.97–4.03 (1H, m, C*H*HO), 4.27 (1H, d, *J* 6.5, CH*HO*) and 4.69–4.75 (1H, m, CHO); δ_C (63 MHz; $CDCl_3$) 19.8, 25.6, 26.9, 30.6, 69.2, 74.7 and two quaternary carbons not apparent in J modulation experiment (JMOD) spectrum; *m*/*z* (EI) 174 (M^+, 37%), 74 (100).

(2*R*)-2-[(2-Methylprop-2-enyl)thio]propan-1-ol 35a

To a mixture of (2*R*)-2-mercaptopropanol **34a** (670 mg, 7.23 mmol) and sodium methoxide (429 mg, 7.95 mmol) in methanol (14 cm^3) at 0 °C was added methallyl bromide (976 mg, 7.23 mmol). The solution was stirred at 0 °C for 1 h and at RT for 3 h, after which it was concentrated under reduced pressure. The residue was suction filtered (with ether washings). The organic filtrate was washed with brine (10 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ether–petrol 20 : 80) to afford **35a** (760 mg, 72%) as a pale yellow oil; $[\alpha]_D^{22} = -5.3$ (*c* 1.13 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3384, 3077, 2970, 2928, 2870 and 1648; δ_H (250 MHz; $CDCl_3$) 1.24 (3H, d, *J* 7, CH_3CH), 1.81 (3H, s, $CH_3C{=}CH_2$), 2.15 (1H, br s, OH), 2.75–2.88 (1H, m, CHS), 3.07 (1H, dd, *J* 14.0 and 1.0, C*H*HS), 3.18 (1H, dd, *J* 14.0 and 1.0, C*H*HS), 3.47 (1H, dd, *J* 11.0 and 6.0, C*H*HO), 3.59 (1H, dd, *J* 11.0 and 5.0, C*H*HO) and 4.81–4.84 (2H, m, $C{=}CH_2$); δ_C (63 MHz; $CDCl_3$) 17.9, 20.7, 38.1, 42.4, 65.4, 113.6 and 141.6; *m*/*z* (EI) 146 (M^+, 100%), 115 (78), 81 (33), 59 (42) and 55 (84) (Found: M^+, 146.0758. $C_7H_{14}OS$ requires M^+, 146.0765).

(2*R*)-3-Methyl-2-[(2-methylprop-2-enyl)thio]butan-1-ol 35b

To a mixture of (2*R*)-3-methyl-2-mercaptobutanol **34b** (2.9 g, 24.1 mmol) and sodium methoxide (1.43 g, 26.5 mmol) in methanol (48 cm^3) at 0 °C was added methallyl bromide (3.25 g, 24.1 mmol). The solution was stirred at 0 °C for 1 h and at RT for 3 h, after which it was concentrated under reduced pressure. The residue was suction filtered (with ether washings). The organic filtrate was washed with brine (10 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ether–petrol 20 : 80) to afford **35b** (2.7 g, 64%) as a pale yellow oil; ν_{max} (film)/cm^{-1} 3385, 3077, 2960, 2873, 1648 and 1457; δ_H (250 MHz; $CDCl_3$) 0.94–1.00 (6H, m, $(CH_3)_2CH$), 1.82 (3H, s, $CH_3C{=}CH_2$), 1.85–2.00 (1H, m, $(CH_3)_2CH$), 2.18 (1H, br s, OH), 2.48–2.55 (1H, m, CHS), 3.06 (1H, dd, *J* 13.0 and 1.0, C*H*HS), 3.16 (1H, dd, *J* 13.0 and 1.0, C*H*HS), 3.53 (1H, dd, *J* 11.0 and 7.0, C*H*HO), 3.68 (1H, dd, *J* 11.0 and 5.0, C*H*HO) and 4.80–4.84 (2H, m, $C{=}CH_2$); δ_C (63 MHz; $CDCl_3$) 19.5, 20.4, 20.6, 29.6, 39.5, 55.4, 62.6, 113.8 and 141.5; *m*/*z* (CI) 175 ([M + H]$^+$, 100%), 157 (6), 143 (20), 109 (6), 87 (18) and 55 (10) (Found: [M + H]$^+$, 175.1158. $C_9H_{19}OS$ requires [M + H]$^+$, 175.1157).

(5*R*)-2-(Iodomethyl)-2,5-dimethyl-1,4-oxathiane 38a

To a solution of sulfide **35a** (260 mg, 1.78 mmol) in carbon tetrachloride (10 cm^3) and water (10 cm^3) was added anhydrous sodium bicarbonate (600 mg, 7.13 mmol) followed by iodine (910 mg, 3.57 mmol). The resulting mixture was stirred at RT for 4 h then diluted with CH_2Cl_2 (20 cm^3) and treated with saturated Na_2SO_3. The organic layer was washed with brine (10 cm^3), dried ($MgSO_4$) and purified by flash column chromatography (ether–petrol 20 : 80) to afford **38a** (390 mg, 80%) as a yellow oil and as a 1 : 1 mixture of diastereoisomers; ν_{max} (film)/cm^{-1} 2960, 2926, 2864 and 1451; δ_H (250 MHz; $CDCl_3$) 1.14 (3H, d, *J* 7, CH_3CH), 1.49 (3H, s, CH_3), 2.51 (1H, d, *J* 13.5, C*H*HS), 2.74–2.89 (1H, m, CH_3CHS), 2.87 (1H, d, *J* 13.5, C*H*HS), 3.27 (1H, d, *J* 10.0, C*H*HI), 3.37 (1H, d, *J* 10.0, C*H*HI), 3.54 (1H, dd, *J* 12.0 and 9.5, C*H*HO) and 3.83 (1H, dd, *J* 12.0 and 3.0, C*H*HO); δ_C (63 MHz; $CDCl_3$) 16.1, 17.3, 21.3, 33.8, 34.3, 68.9 and 69.0; *m*/*z* (EI) 272 (M^+, 57%), 185 (12), 145 (27), 103 (68), 87 (77), 59 (83) and 55 (100) (Found: M^+, 271.9732. $C_7H_{13}IOS$ requires M^+, 271.9732).

(5*R*)-2-(Iodomethyl)-2-methyl-5-(1-methylethyl)-1,4-oxathiane 38b

To a stirred solution of **35b** (2.46 g, 14.1 mmol) in acetonitrile (160 cm^3) was added anhydrous sodium carbonate (15 g, 141 mmol) and iodine (18 g, 70.7 mmol). The mixture was stirred in the dark at RT for 8 h, diluted with ether (100 cm^3) and then treated with an aqueous solution of Na_2SO_3 (10% w/v). The organic layer was washed with brine (50 cm^3), dried ($MgSO_4$) and purified by flash column chromatography (ether–petrol 20 : 80) to afford **38b** (2.3 g, 55%) as a yellow oil and as a 1 : 1 mixture of diastereoisomers; ν_{max} (film)/cm^{-1} 2959, 2931, 2871, 1463 and 1360; δ_H (250 MHz; $CDCl_3$, mixture of diastereoisomers) 0.95–1.01 (12H, m, $2(CH_3)_2CH$), 1.32 and 1.46 (6H, 2s, $2CH_3$), 1.64–1.83 (2H, m, $2(CH_3)_2CH$), 2.42–2.93 (6H, m, $2CH_2S$ and 2CHS) and 3.24–3.94 (8H, m, $2CH_2I$ and $2CH_2O$); δ_C (63 MHz; $CDCl_3$, mixture of diastereomers denoted as unmarked and *) 13.0, 17.4*, 20.0, 20.1, 20.2*, 20.3*, 21.5, 27.8*, 29.0, 29.4*, 34.2, 34.3*, 46.4, 46.5*, 65.9, 66.1*, 69.0 and 69.4*; *m*/*z* (CI, NH_3) 301 ([M + H]$^+$, 100%), 283 (5), 173 (55), 117 (20) and 69 (17) (Found: [M + H]$^+$, 301.0119. $C_9H_{17}IOS$ requires [M + H]$^+$, 301.0123).

Ethyl (2*R*,3*S*)-3-hydroxytetrahydro-2*H*-thiopyran-2-carboxylate 40

A conical flask containing tap water (200 cm^3) was kept in a water bath at 30 °C for 1 h, after which Baker's yeast (25 g) was added and the mixture kept at the same temperature for 40 min. β-Ketoester **39** (1.0 g, 5.3 mmol) was added (with ethanol washing, 1 cm^3) and this mixture was kept at 30 °C for 66 h. The reaction mixture was filtered under vacuum through Hyflo supercel (with water washing, 50 cm^3). The aqueous filtrate was extracted with ether (3 × 250 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate–petrol 10 : 90) afforded **40** (669 mg, 66%) as a light beige amorphous solid. Recrystallisation from ether–hexane at −20 °C gave clear needles; $[\alpha]_D^{22}$ −64.5 (*c* 1.07 in $CHCl_3$) (Found: C, 50.4; H, 7.3; S, 16.7. $C_8H_{14}O_3S$ requires C, 50.5; H, 7.4; S, 16.9%); ν_{max} (Nujol)/cm^{-1} 3330 and 1719; δ_H (250 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.0, OCH_2CH_3), 1.65–1.88 (2H, m, CH_2), 1.97–2.10 (2H, m, CH_2), 2.44–2.90 (3H, m, CH_2S and OH), 3.68 (1H, d, *J* 3.0, CH), 4.15–4.22 (1H, m, CH) and 4.23 (2H, q, *J* 7.0, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 14.1, 24.3, 26.6, 31.2, 47.8, 61.5, 67.1 and 170.9; *m*/*z* (EI) 190 (M^+, 90%), 144 (86), 117 (78) and 71 (100).

Crystal structure of 40. Crystal data for $C_8H_{14}O_3S$; M = 190.25. Crystallises from *n*-hexane as colourless blocks; crystal dimensions 0.42 × 0.31 × 0.14 mm^3. Orthorhombic, $a = 5.2525(19)$, $b = 10.029(4)$, $c = 17.826(7)$ Å, $U = 939.0(6)$ Å^3, $Z = 4$, $D_C = 1.346$ Mg m^{-3}, space group $P2_12_12_1$ (D_2^4, no. 19), Mo-Kα radiation (λ = 0.71073 Å), μ(Mo-Kα) = 0.311 mm^{-1}, $F(000) = 408$. CCDC reference number 1685533. See http://www.rsc.org/suppdata/p1/b1/b105416n/ for crystallographic files in .cif or other electronic format.

(2*S*,3*S*)-2-(Hydroxymethyl)tetrahydro-2*H*-thiopyran-3-ol 41

To a solution of ester **40** (500 mg, 2.63 mmol) in ether (8 cm^3) at 0 °C was added lithium aluminium hydride (500 mg, 13.2 mmol). The mixture was warmed to RT and then refluxed for 18 h. At 0 °C, iced water (4 cm^3), dilute HCl solution (4 cm^3, 3% v/v), potassium sodium tartrate (2 g) and ethyl acetate (20 cm^3) were sequentially added. The mixture was stirred rapidly for 10 min, extracted with ethyl acetate (3 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 50 : 50) to afford **41** (295 mg, 76%) as a white solid; $[\alpha]_D^{22}$ = −51.8 (*c* 1.1 in $CHCl_3$) (Found: C, 48.4; H, 8.3; S, 21.9. $C_6H_{12}O_2S$ requires C, 48.6; H, 8.2; S, 21.6%); ν_{max} (Nujol)/cm^{-1} 3394 and 3318; δ_H (250 MHz; $CDCl_3$) 1.52–1.66 (1H, m, C*H*H), 1.78–2.06 (3H, m, CH*H* and CH_2), 2.48 (1H, dd, *J* 6.5 and 5.0, CH_2OH), 2.55–2.59 (2H, m, CH_2S), 2.90 (1H, d, *J* 9.0, CHO*H*), 3.11 (1H, dt, *J* 6.5 and 2.0, CHS), 3.74–3.93 (2H, m, C*H*$_2$OH) and 4.10–4.16 (1H, m, C*H*OH); δ_C (63 MHz; $CDCl_3$) 22.9, 27.2, 32.1, 48.6, 63.1 and 66.7; *m*/*z* (EI) 148 (M^+, 88%), 130 (88), 117 (87), 87 (100).

(2*R*,3*S*)-2-(1-Hydroxy-1-methylethyl)tetrahydro-2*H*-thiopyran-3-ol 42

To a solution of ester **40** (405 mg, 2.13 mmol) in ether (25 cm^3) at 0 °C was added methylmagnesium bromide (4 cm^3, 12 mmol, 3 M in ether). The mixture was warmed to RT and stirred for 18 h. At 0 °C, saturated ammonium chloride solution (10 cm^3) was added to the solution and the separated aqueous layer extracted with ether (3 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 30 : 70) to afford **42** (280 mg, 75%) as a white solid, mp 78–80 °C; $[\alpha]_D^{28}$ = −25.5 (*c* 0.98 in CH_2Cl_2); ν_{max} (Nujol)/cm^{-1} 3224; δ_H (250 MHz; $CDCl_3$) 1.32 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.39–1.51 (1H, m, C*H*H), 1.69–2.03 (3H, m, CH*H* and CH_2), 2.55–2.70 (4H, m, CH_2 and OH), 2.87 (1H, d, *J* 1.0, CH) and 4.30–4.36 (1H, m, CH); δ_C (63 MHz; $CDCl_3$) 20.8, 28.3, 28.6, 29.0, 33.7, 57.9, 64.6 and 73.0; *m*/*z* (EI) 176 (M^+, 12%), 158 (34), 100 (100), 85 (44) and 58 (56) (Found: M^+, 176.0867. $C_8H_{16}O_2S$ requires M^+, 176.0871).

Ethyl (2*R*,3*S*)-3-hydroxy-2-methyltetrahydro-2*H*-thiopyran-2-carboxylate 43

To a solution of freshly prepared lithium diisopropylamide (19.16 mmol) in THF (7 cm^3) at −50 °C was added a solution of ester **40** (1.5 g, 7.90 mmol) in THF (9 cm^3). The mixture was slowly warmed to −15 °C and methyl iodide (0.64 cm^3, 10.26 mmol) in HMPA (5.9 cm^3) was added. The mixture was stirred at −15 °C for 1.5 h. Saturated ammonium chloride solution (15 cm^3) was added to the solution and the separated aqueous layer extracted with ether (3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 10 : 90) to afford **43** (1.31 g, 81%) as a colourless oil and an inseparable mixture of diastereomers (ratio of 6 : 1 in favour of **43**); $[\alpha]_D^{23}$ = −55.9 (*c* 0.93 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3449, 2931 and 1720; δ_H (250 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.0, OCH_2CH_3), 1.55 (3H, s, CH_3), 1.63–2.11 (4H, m, $2CH_2$), 2.36–2.44 (1H, m, C*H*HS), 2.53–2.65 (1H, m, CH*H*S), 2.76 (1H, br s, OH), 3.65 (1H, m, CH) and 4.22 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$); δ_C (63 MHz; $CDCl_3$) 14.1, 23.2, 27.0, 27.2, 31.0, 51.4, 61.5, 75.0 and 174.0; *m*/*z* (EI) 204 (M^+, 65%), 158 (100), 131 (78) and 71 (100) (Found: M^+, 204.0822. $C_9H_{16}O_3S$ requires M^+, 204.0820).

(2*S*,3*S*)-2-(Hydroxymethyl)-2-methyltetrahydro-2*H*-thiopyran-3-ol 44

To a solution of ester **43** (1.2 g, 5.9 mmol) in ether (18 cm^3) at 0 °C was added lithium aluminium hydride (1.2 g, 29.4 mmol) portionwise. The mixture was warmed to RT and then refluxed for 18 h. At 0 °C, iced water (9 cm^3), dilute HCl (9 cm^3, 3% v/v), potassium sodium tartrate (2 g) and ethyl acetate (30 cm^3) were sequentially added. The mixture was stirred rapidly for 10 min, extracted with ethyl acetate (3 × 40 cm^3). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 50 : 50) to afford **44** (738 mg, 77%) as a white solid and as an inseparable mixture of diastereomers; $[\alpha]_D^{23}$ = −36.7 (*c* 0.98 in $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 3333; δ_H (250 MHz; $CDCl_3$) 1.42 (3H, s, CH_3), 1.60–1.91 (3H, m, CH_2 and C*H*H), 2.02–2.11 (1H, m, CH*H*), 2.26 (2H, br s, 2OH), 2.46–2.68 (2H, m, CH_2S), 3.71 (1H, d, *J* 11.0, C*H*H), 3.84 (1H, dd, *J* 9.0 and 3.0, CH) and 3.97 (1H, d, *J* 11.0, CH*H*); δ_C (63 MHz; $CDCl_3$) 22.4, 25.3, 26.3, 30.0, 46.9, 66.4 and 75.6; *m*/*z* (EI) 162 (M^+, 34%), 131 (100) (Found: M^+, 162.0707. $C_7H_{14}O_2S$ requires M^+, 162.0715).

(2*S*,5*R*)-2-Methyl-5-(1-methylethenyl)-2-[(phenylmethyl)thio]-cyclohexan-1-one 50

To a solution of silyl enol ether **49** (3.66 g, 16.35 mmol) in THF (33 cm^3) at 0 °C was added methyllithium (10.3 cm^3, 16.35 mmol, 1.58 M in ether) dropwise. The solution was stirred at 0 °C for 1 h and was then added *via* cannula to a solution of benzylthiotosylate (5.0 g, 17.99 mmol) and HMPA (8.5 cm^3, 49.05 mmol) in THF (33 cm^3) at −78 °C. The mixture was stirred at this temperature for 3.5 h, after which saturated ammonium chloride solution (10 cm^3) was added to the solution and the separated aqueous layer extracted with ether (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 2.5 : 97.5) to afford **50** (3.75 g, 84%) as a colourless oil and an inseparable mixture of diastereomers (ratio of 4 : 1 in favour of **50**); $[\alpha]_D^{18}$ = +167.3 (*c* 0.55 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2929, 1698 and 1452; δ_H (250 MHz; $CDCl_3$, major diastereomer) 1.29 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.58–2.16 (6H, m, CH and CH_2), 2.95–3.07 (1H, m, CH), 3.25 (1H, d_{AB}, *J* 12.0, C*H*HS), 3.54 (1H, d_{AB}, *J* 12.0, CH*H*S), 4.49–4.74 (2H, m, CH_2=) and 7.04–7.17 (5H, m, CH); δ_C (63 MHz; $CDCl_3$) 20.4, 23.6, 26.4, 33.4, 39.3, 41.6, 46.3, 54.0, 109.9, 127.2, 128.6, 129.1, 137.1 and 147.3; *m*/*z* (EI) 274 (M^+, 31%), 152 (100), 109 (73), 91 (67) (Found: M^+, 274.1404. $C_{17}H_{22}OS$ requires M^+, 274.1391).

(1*R*,2*S*,5*R*)-2-Methyl-5-(1-methylethenyl)-2-[(phenylmethyl)-thio]cyclohexan-1-ol 51

To a solution of ketone **50** (6.0 g, 21.9 mmol) in CH_2Cl_2 (100 cm^3) at −78 °C was added DIBAL-H (32.8 cm^3, 32.8 mmol, 1 M in hexane). The solution was stirred at this temperature for 2 h, after which methanol (5 cm^3), water (20 cm^3) and potassium sodium tartrate (1.5 g) were sequentially added. The mixture was stirred rapidly for 10 min, extracted with ether (3 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 5 : 95 to 20 : 80) to afford **51** (4.05 g, 67%) as a white solid; $[\alpha]_D^{18}$ = +32.6 (*c* 0.46 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3347, 2928, 2362 and 1450; δ_H (250 MHz; $CDCl_3$) 1.32–1.94 (7H, m, CH and CH_2), 1.43 (3H, s, CH_3), 1.64 (3H, s, CH_3), 3.30 (1H, m, C*H*OH), 3.69 (1H, d_{AB}, *J* 12.0, C*H*HS), 3.76 (1H, d_{AB}, *J* 12.0, CH*H*S), 4.60–4.65 (2H, m, CH_2) and 7.16–7.31 (5H, m, CH); δ_C (63 MHz; $CDCl_3$) 20.9, 26.7, 27.0, 32.6, 36.4, 38.2, 44.2, 53.6, 78.1, 109.0, 127.1, 128.6, 129.1, 138.5 and 148.8; *m*/*z* (EI) 276 (M^+, 25%), 185 (100) (Found: M^+, 276.1559. $C_{17}H_{24}OS$ requires M^+, 276.1548).

(1*R*,2*S*,5*R*)-2-(2,2-Diethoxyethylthio)-2-methyl-5-(1-methylethenyl)cyclohexan-1-ol 53

Ammonia (105 cm^3) was condensed into a three-necked flask at −78 °C. Sodium pieces (1.71 g, 74.1 mmol) were added to the mixture, which was then stirred for 30 min. A solution of sulfide **51** (3.9 g, 14.1 mmol) in THF (47 cm^3) was added to the mixture, which was kept at −78 °C for 50 min. Methanol (25 cm^3) and saturated ammonium chloride solution (50 cm^3) were added to the solution, which was warmed to RT for 2 h. The mixture was extracted with ether (3 × 100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to afford **52** (1.93 g) as a white solid, which was used immediately in the next step. A mixture of hydroxythiol **52** (1.93 g, 10.38 mmol), bromoacetaldehyde diethyl acetal (1.7 cm^3, 11.41 mmol) and powdered potassium hydroxide (1.42 g, 25.42 mmol) in 95% ethanol (19 cm^3) was heated at reflux for 16 h. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (ethyl acetate–petrol 5 : 95) to afford **53** (1.65 g, 39% over two steps) as an oil; $[\alpha]_D^{18}$ = +38.1 (*c* 0.21 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3439, 2975, 2931 and 1645; δ_H (250 MHz; $CDCl_3$) 1.22 (3H, t, *J* 7.0, OCH_2CH_3), 1.26 (3H, t, *J* 7.0, OCH_2CH_3), 1.46–1.55 (4H, m, CH and CH_3), 1.73 (3H, s, CH_3), 1.78–2.00 (4H, m, CH_2), 2.76 (1H, dd, *J* 14.0 and 4.5, C*H*HS), 3.00 (1H, dd, *J* 14.0 and 7.0, CH*H*S), 3.08 (1H, d, *J* 10.5, OH), 3.35 (1H, dt, *J* 10.5 and 5.0, C*H*OH), 3.50–3.82 (4H, m, OCH_2CH_3), 4.61 (1H, dd, *J* 7.0 and 4.0, C*H*(OEt)$_2$) and 4.68–4.74 (2H, m, CH_2); δ_C (63 MHz; $CDCl_3$) 15.1, 15.3, 20.8, 26.7, 27.2, 31.1, 36.5, 39.3, 44.5, 52.7, 61.0, 63.2, 78.1, 102.7, 108.8 and 149.0; *m*/*z* (CI) 303 ([M + H]$^+$, 19%), 257 (56), 211 (100), 135 (56) (Found: M^+, 302.1921. $C_{16}H_{30}O_3S$ requires M^+, 302.1916).

(4a*S*,7*R*,8a*R*)-4a-Methyl-7-(1-methylethenyl)-4a,5,6,7,8,8a-hexahydro-1,4-benzoxathiine 54

To a solution of sulfide **53** (500 mg, 1.66 mmol) in ether (8 cm^3) at 0 °C was added $BF_3·OEt_2$ (0.42 cm^3, 3.3 mmol). After 1.5 h $BF_3·OEt_2$ (0.42 cm^3, 3.3 mmol) was added and the solution stirred for a further 2 h. Further $BF_3·OEt_2$ (0.42 cm^3, 3.3 mmol) was added, after which the solution was warmed to RT and stirred for 18 h. The mixture was quenched with water (5 cm^3), extracted with ether (3 × 10 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (hexane) to afford **54** (171 mg, 50%) as a colourless oil; $[\alpha]_D^{18}$ = +328.0 (*c* 0.25 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2918, 2860, 1610 and 1449; δ_H (250 MHz; $CDCl_3$) 1.44 (3H, s, CH_3), 1.49–2.11 (7H, m, CH and CH_2), 1.74 (3H, s, CH_3), 3.72 (1H, dd, *J* 11.0 and 4.0, CHO), 4.70–4.78 (2H, m, CH_2), 4.99 (1H, d, *J* 6.5, CHS) and 6.47 (1H, d, *J* 6.5, CHO); δ_C (63 MHz; $CDCl_3$) 20.7, 26.5, 28.6, 33.7, 37.8, 43.1, 44.5, 78.0, 91.3, 109.3, 135.8 and 148.5; *m*/*z* (EI) 210 (M^+, 73%), 93 (100), 68 (70) (Found: M^+, 210.1088. $C_{12}H_{18}OS$ requires M^+, 210.1078).

(2*S*,6*S*)-2,6-Bis[(methyloxy)methyl]tetrahydro-2*H*-thiopyran 61

To a solution of diol **69** (130 mg, 0.68 mmol) and triethylamine (0.28 cm^3, 2.0 mmol) in CH_2Cl_2 (10 cm^3) at −15 °C was added methanesulfonyl chloride (0.13 cm^3, 1.70 mmol). After 1 h, the mixture was quenched with saturated sodium bicarbonate solution (5 cm^3), extracted with CH_2Cl_2 (3 × 10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude mesylate which was immediately dissolved in DMSO (5 cm^3). Lithium sulfide (40 mg, 0.81 mmol) was added and the mixture was then stirred at 50 °C for 24 h. The mixture was quenched with sodium bicarbonate solution (5 cm^3), extracted with petroleum ether (3 × 10 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ether–petrol 20 : 80) to afford **61** (21 mg, 43% over two steps) as a colourless oil; $[\alpha]_D^{22}$ = +90.0 (*c* 0.70 in $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 1.54–1.66 (2H, m, 2CH), 1.83–1.94 (2H, m, 2CH), 3.05 (2H, m, 2CHS), 3.34 (6H, s, $2OCH_3$) and 3.40–3.55 (4H, m, $2CH_2O$); δ_C (63 MHz; $CDCl_3$) 20.2, 28.9, 37.8, 58.8 and 75.1; *m*/*z* (CI) 191 ([M + H]$^+$, 100%), 159 (45), 145 (30), 113 (55) (Found: [M + H]$^+$, 191.1106. $C_9H_{19}O_2S$ requires [M + H]$^+$, 191.1106).

(2*R*,6*R*)-6-(Hydroxymethyl)tetrahydro-2*H*-pyran-2-ylmethanol 62

To a flask containing liquid ammonia (25 cm^3) at −78 °C was added sodium metal (250 mg, 11 mmol) portionwise. Sulfide **76** (251 mg, 0.7 mmol) in THF (4 cm^3) was added dropwise and the reaction was allowed to stir at −78 °C for 1.5 h. The reaction was then quenched by the addition of absolute ethanol (20 cm^3) and diluted with ether (20 cm^3) before allowing the reaction to warm to RT and the ammonia to subsequently evaporate. The aqueous layer was extracted with ether (3 × 20 cm^3). The combined extracts were washed with brine (10 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 50 : 50) to afford **62** (64 mg, 54%) as a white solid, mp 58–59 °C; $[\alpha]_D^{25.5}$ = −112.8 (*c* 0.47 in $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3331, 2940 and 2870; δ_H (250 MHz; $CDCl_3$) 1.50–1.64 (2H, m, CH_2), 1.65 (2H, m, CH_2), 1.85–2.00 (2H, br m, CH_2), 2.70 (2H, s, 2OH), 2.90–3.05 (2H, br m, CH_2) and 3.60–3.65 (4H, m, $2CH_2OH$); δ_C (63 MHz; $CDCl_3$) 20.9, 29.0, 41.1 and 64.4; *m*/*z* (EI) 162 (M^+, 23%), 131 (100), 113 (60), 79 (53), 67 (28) (Found: M^+, 162.0707. $C_7H_{14}O_2S$ requires M^+, 162.0714).

(2*R*,6*R*)-2,6-Dimethyl-4-(phenylsulfonyl)tetrahydro-2*H*-thiopyran 63

A mixture of lithium sulfide (180 mg, 3.93 mmol) in DMF (3 cm^3) was heated at reflux for 15 min, before being cooled to RT. Dimesylate **79** (285 mg, 0.67 mmol) was added and the mixture was stirred for 50 h, after which water (15 cm^3) was added. The mixture was extracted with ether (3 × 10 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 50 : 50) to afford **63** (145 mg, 81%) as clear crystals, mp 106.5–108 °C; $[\alpha]_D^{25}$ = +36.9 (*c* 1.6 in $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 2923, 1305 and 1284 (Found: C, 57.8; H, 6.7; S, 23.7. $C_{13}H_{18}O_2S_2$ requires C, 57.6; H, 6.5; S, 23.8%); δ_H (250 MHz; $CDCl_3$) 1.24 (3H, d, *J* 7.0, CH_3), 1.34 (3H, d, *J* 6.5, CH_3), 1.19–1.35 (1H, m, C*H*H), 1.81 (1H, dt, *J* 13.0 and 4.5, CH*H*), 2.16 (1H, m, C*H*H), 2.34 (1H, m, CH*H*), 2.94 (1H, m, $CHSO_2Ph$), 3.14 (2H, m, $2CHCH_3$), 7.52 (2H, m, CH), 7.63 (1H, m, CH) and 7.79 (2H, m, CH); δ_C (63 MHz; $CDCl_3$) 20.8, 21.2, 31.3, 32.2, 34.1, 35.7, 59.5, 129.2, 129.2, 133.9 and 136.3; *m*/*z* (EI) 270 (M^+, 43%), 128 (100) and 113 (75).

(2*R*)-1-{2-[(2*R*)-2-Hydroxy-3-methoxypropyl]-1,3-dithian-2-yl}-3-methoxypropan-2-ol 68

To a solution of dithiane **66** (1.06 g, 4.5 mmol) and HMPA (4 cm^3) in THF (30 cm^3) at −78 °C was added dropwise *tert*-butyllithium (4.5 cm^3, 6.8 mmol, 1.5 M in pentane). (*S*)-Glycidyl methyl ether **67** (1.0 g, 11.3 mmol) was then added and the solution warmed to −40 °C and stirred for 1.5 h. The mixture was quenched with saturated ammonium chloride solution (10 cm^3), extracted with ether (3 × 30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to afford a crude product which was immediately dissolved in THF (10 cm^3). Excess TBAF (1 M solution in THF) was added at 0 °C and the mixture was stirred at RT for 30 min. The mixture was quenched with saturated ammonium chloride solution (5 cm^3), extracted with ether (3 × 15 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (EtOAc–petrol 60 : 40) to afford **68** (850 mg, 63% over two steps) as a colourless oil; $[\alpha]_D^{25}$ = +20.6 (*c* 0.97 in $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 1.91–2.00 (2H, m, CH_2), 2.14–2.31 (4H, m, $2CH_2$), 2.72–2.83 (4H, m, $2CH_2S$), 3.32 (4H, d, *J* 5.5, $2CH_2OCH_3$), 3.38 (6H, s, $2OCH_3$), 3.66 (2H, br s, 2OH) and 4.13–4.23 (2H, m, 2C*H*OH); *m*/*z* (CI) 297 ([M + H]$^+$, 100%), 279 (45), 223 (65) and 207 (55) (Found: [M + H]$^+$, 297.1197. $C_{12}H_{24}O_4S_2$ requires [M + H]$^+$, 297.1194).

(2*R*,6*R*)-1,7-Dimethoxyheptane-2,6-diol 69

To a solution of diol **68** (850 mg, 2.87 mmol) in ethanol (1 cm^3) at RT was added a solution of freshly prepared Raney nickel (10 cm^3). The mixture was stirred for 72 h, after which it was filtered through Celite, concentrated under reduced pressure and purified by flash column chromatography (MeOH–CH_2Cl_2 10 : 90) to afford **69** (150 mg, 27%) as a colourless oil; ν_{max} (film)/cm^{-1} 3416; δ_H (250 MHz; $CDCl_3$) 1.35–1.58 (6H, m, 3CH_2), 2.40 (2H, br s, 2OH), 3.22 (2H, dd, *J* 9.5 and 7.9, 2C*H*HO), 3.36 (6H, s, 2OCH_3), 3.40 (2H, dd, *J* 7.9 and 3.0, 2CH*H*O) and 3.76 (2H, m, 2C*H*OH); δ_C (63 MHz; $CDCl_3$) 21.6, 36.4, 59.0, 70.1 and 77.0; *m*/*z* (CI) 193 ([M + H]$^+$, 100%), 175 (20), 129 (55), 97 (15) (Found: [M + H]$^+$, 193.1441. $C_9H_{21}O_4$ requires [M + H]$^+$, 193.1440).

(2*S*,6*S*)-1,7-Bis(benzyloxy)-4-(phenylsulfonyl)heptane-2,6-diol 73

To a solution of sulfone **70** (782 mg, 5.0 mmol) in THF (19 cm^3) and HMPA (1 cm^3) at −78 °C was added *n*-butyllithium (7 cm^3, 11.2 mmol, 1.6 M in hexane) dropwise. The resulting orange solution was stirred at −78 °C for 1 h before the addition of (*R*)-(+)-benzyl glycidyl ether **71** (1.66 g, 10 mmol). The reaction was stirred at −78 °C for 3 h and then at RT for 18 h, after which it was quenched by the addition of saturated ammonium chloride solution (10 cm^3). The mixture was extracted with ether (3 × 30 cm^3), washed with water (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 50 : 50) to afford **73** (1.22 g, 50%) as white needles and mono-alkylated **72** (639 mg, 40%), mp 42–44 °C (EtOAc); $[\alpha]_D^{24.5}$ = −21.6 (*c* 1.16 in $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3466, 3427, 2930, 2868 and 1448; δ_H (250 MHz; $CDCl_3$) 1.55–1.75 (2H, m, CH_2), 1.85 (1H, ddd, *J* 13.6, 10.4 and 3.1, CH), 2.20 (1H, ddd, *J* 15.6, 6.3 and 2.6, CH), 3.05 (1H, br s, OH), 3.15–3.20 (1H, br d, *J* 4.0, OH), 3.25–3.50 (4H, m, CH_2), 3.50–3.60 (1H, m, CH), 3.85–4.00 (2H, m, CH_2), 4.50 (4H, s, 2C*H*$_2$Ph), 7.20–7.40 (10H, m, 2*Ph*CH_2O), 7.45–7.60 (2H, m, $PhSO_2$), 7.60–7.70 (1H, m, $PhSO_2$) and 7.80–7.90 (2H, m, $PhSO_2$); δ_C (63 MHz; $CDCl_3$) 30.7, 33.0, 58.1, 66.3, 69.3, 73.3, 73.35, 73.8, 73.9, 127.5, 127.6, 127.7, 128.2, 128.3, 128.8, 129.1, 133.6, 137.3, 137.7 and 137.9; *m*/*z* (EI) 484 (M^+, 1%), 287 (50), 113 (28) and 91 (100) (Found: M^+, 484.1896. $C_{27}H_{32}O_6S$ requires M^+, 484.1920).

(2*S*,6*S*)-1,7-Bis(benzyloxy)heptane-2,6-diol 74

To a solution of diol **73** (2.39 g, 4.9 mmol) in methanol (45 cm^3) was added successively anhydrous sodium hydrogen phosphate (dibasic) (3.18 g) and sodium amalgam (24.1 g, 4%). The reaction was stirred vigorously for 3 h before it was poured into water (200 cm^3) and the aqueous layer extracted with ether (4 × 100 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford **74** (1.46 g, 86%) as a colourless oil; $[\alpha]_D^{22}$ = +3.6 (*c* 1.93 in $CHCl_3$) [lit. $[\alpha]_D$ = −4.8 (*c* 1.19 in $CHCl_3$) *ent*]; ν_{max} (film)/cm^{-1} 3420, 2918, 2861, 1496 and 1453; δ_H (250 MHz; $CDCl_3$) 1.35–1.55 (6H, m, 3CH_2), 2.35–2.60 (2H, br s, 2OH), 3.30 (2H, dd, *J* 9.2 and 7.9, 2CH), 3.50 (2H, dd, *J* 9.3 and 3.2, 2CH), 3.75–3.90 (2H, m, 2CH), 4.55 (4H, s, 2PhC*H*$_2$) and 7.25–7.40 (10H, m, 2Ph); δ_C (63 MHz; $CDCl_3$) 21.6, 33.0, 70.2, 73.3, 74.7, 127.8, 128.5 and 138.0; *m*/*z* (CI) 362 ([M + NH_4]$^+$, 71%), 222 (61), 219 (41), 108 (40) and 106 (100) (Found: [M + H]$^+$, 345.2081. $C_{21}H_{29}O_4$ requires [M + H]$^+$, 345.2066).

(2*S*,6*S*)-1,7-Bis(benzyloxy)-2,6-bis[(*p*-tolylsulfonyl)oxy]heptane 75

To a solution of diol **74** (1.46 g, 4.25 mmol) in CH_2Cl_2 (20 cm^3) were added successively triethylamine (1.9 cm^3, 13.6 mmol), toluene-*p*-sulfonyl chloride (2.5 g, 13.1 mmol) and DMAP (132 mg, 1.2 mmol). The reaction was stirred at RT for 18 h before being diluted with ether (30 cm^3) and filtered through Celite. The filtrate was washed with brine (3 × 40 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 20 : 80) to afford **75** (2.45 g, 88%) as a colourless oil; $[\alpha]_D^{22}$ = −6.35 (*c* 1.89 in $CHCl_3$) [lit., $[\alpha]_D$ = +3.9 (*c* 1.35 in $CHCl_3$) *ent*]; ν_{max} (film)/cm^{-1} 2924, 2867, 1598 and 1496; δ_H (250 MHz; $CDCl_3$) 1.10–1.30 (2H, m, CH_2), 1.55–1.70 (4H, m, 2CH_2), 2.40 (6H, s, 2CH_3), 3.35–3.50 (4H, m, 2CH_2), 4.34 (2H, d_{AB}, *J* 12.1, 2C*H*Ph), 4.42 (2H, d_{AB}, *J* 12.1, 2C*H*Ph), 4.55 (2H, m, 2CH), 7.15–7.35 (14H, m, Ar) and 7.70–7.80 (2H, m, Ar); δ_C (63 MHz; $CDCl_3$) 20.0, 21.7, 31.2, 70.6, 73.3, 81.2, 127.7, 127.8, 127.9, 128.4, 128.5, 129.7, 129.8, 134.1, 137.7 and 144.6; *m*/*z* (CI) 670 ([M + NH_4]$^+$, 20%), 498 (100), 408 (53), 280 (52), 190 (51) and 108 (53) (Found: [M + NH_4]$^+$, 670.7748. $C_{35}H_{44}NO_8S_2$ requires [M + NH_4]$^+$, 670.2508).

(2*R*,6*R*)-2,6-Bis[(benzyloxy)methyl]tetrahydro-2*H*-thiopyran 76

A mixture of lithium sulfide (1.05 g, 23 mmol) in DMF (6 cm^3) was heated at 70 °C for 45 min. Bis(toluene-*p*-sulfonate) **75** (2.45 g, 3.8 mmol) was subsequently added and the reaction was maintained at 70 °C for 72 h. Following cooling to RT the mixture was poured into water (40 cm^3) and extracted with ether (3 × 40 cm^3). The combined organic extracts were washed with brine (40 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 5 : 95) to afford **76** (558 mg, 43%) as a colourless oil; $[\alpha]_D^{26}$ = −19.7 (*c* 1.5 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3030, 2927, 2856 and 1496; δ_H (250 MHz; $CDCl_3$) 1.60 (2H, q, *J* 5.7, CH_2), 1.65–2.00 (4H, m, 2CH_2), 3.00–3.15 (2H, m, 2CH), 3.55 (2H, d, *J* 6.0, 2CH), 3.57 (2H, d, *J* 6.0, 2CH), 4.52 (2H, d_{AB}, *J* 6.0, 2C*H*Ph), 4.56 (2H, d_{AB}, *J* 6.0, 2C*H*Ph) and 7.25–7.40 (10H, m, aryl); δ_C (63 MHz; $CDCl_3$) 20.1, 29.1, 38.0, 72.5, 73.1, 127.7, 127.7, 128.4 and 138.2; *m*/*z* (EI) 342 (M^+, 1%), 234 (40), 145 (38) and 91 (100) (Found: M^+, 342.1653. $C_{21}H_{26}O_2S$ requires M^+, 342.1654).

(2*S*,6*S*)-4-(Phenylsulfonyl)heptane-2,6-diol 78

To a solution of sulfone **70** (1.30 g, 8.32 mmol) in THF (25 cm^3) at 0 °C was added *n*-butyllithium (7.3 cm^3, 18.3 mmol, 2.5 M in hexane) dropwise. The mixture was cooled to −78 °C, HMPA (2.5 cm^3) was added and the solution was stirred for 1 h. Pre-cooled (−78 °C) (*S*)-(−)-propylene oxide (966 mg, 16.6 mmol) was added to the mixture, which was kept at −78 °C for 2 h, after which it was warmed slowly to RT and stirred for 72 h. The mixture was quenched with water (15 cm^3), extracted with ether (3 × 20 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (EtOAc–petrol 50 : 50) to afford **78** (1.32 g, 58%) as a colourless oil and monoalkylated **77** (420 mg); $[\alpha]_D^{25}$ = +41.9 (*c* 2.6 in $CHCl_3$) [lit. $[\alpha]_D$ = +50.0 (*c* 1.19 in $CHCl_3$)]; ν_{max} (film)/cm^{-1} 3410, 2969, 1709 and 1447; δ_H (250 MHz; $CDCl_3$) 1.13 (6H, m, 2CH_3), 1.50–1.75 (3H, m, CH_2 and C*H*H), 2.10 (1H, ddd, *J* 6.5, 4.0 and 2.5, CH*H*), 3.40 (1H, m, C*H*SO_2Ph), 3.83 (2H, m, C*H*OH), 7.52 (2H, m, CH), 7.61 (1H, m, CH) and 7.84 (2H, m, CH); δ_C (63 MHz; $CDCl_3$) 23.2, 23.9, 35.1, 38.0, 59.0, 63.2, 67.8, 128.9, 129.3, 133.8 and 137.2; *m*/*z* (CI) 273 ([M + H]$^+$, 100%) (Found: [M + H]$^+$, 273.1158. $C_{13}H_{21}O_4S$ requires [M + H]$^+$, 273.1161).

(1*S*,5*S*)-1-Methyl-5-[(methylsulfonyl)oxy]-3-(phenylsulfonyl)-hexyl methanesulfonate 79

To a solution of diol **78** (397 mg, 1.46 mmol) in CH_2Cl_2 (4 cm^3) at −10 °C were added sequentially triethylamine (0.51 cm^3, 3.65 mmol) and methanesulfonyl chloride (0.28 cm^3, 3.65 mmol). The mixture was stirred for 1 h, after which HCl solution (1.5 cm^3, 3% v/v) was added. The mixture was extracted with CH_2Cl_2 (3 × 5 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (ethyl acetate–petrol 50 : 50) to afford **79** (297 mg, 41%) as a white solid, mp 127.5–130 °C; $[\alpha]_D^{25}$ = +0.4 (*c* 2.15 in $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 2923 and 1461 (Found: C, 42.1; H, 5.6; S, 22.4. $C_{15}H_{24}O_8S_3$ requires C, 41.8; H, 5.5; S, 22.5%); δ_H (250 MHz; $CDCl_3$) 1.32 (3H, d, *J* 6.5, CH_3), 1.38 (3H, d, *J* 6.5, CH_3), 1.61 (1H, m, C*H*H), 1.60–1.95 (2H, m, CH_2), 2.28 (1H, m, CH*H*), 2.86 (3H, s, CH_3), 3.05 (3H, s, CH_3), 3.47 (1H, m, $CHSO_2Ph$), 4.75 (1H, m, CHOMs), 5.23 (1H, m, CHOMs), 7.54 (2H, m, CH), 7.64 (1H, m, CH) and 7.88 (2H, m, CH); δ_C (63 MHz; $CDCl_3$) 21.6, 21.8, 35.9, 36.9, 38.2, 38.8, 56.3, 74.9, 76.6, 128.8, 129.4, 134.2 and 137.0; *m*/*z* (CI) 446 ($[M + NH_4]^+$, 59%).

General procedure for the epoxidation of benzaldehyde using catalytic quantities of sulfide

To a 5 cm^3 round-bottomed flask fitted with a nitrogen balloon and containing a magnetic stirrer bar were added sequentially sulfide (20 mol%), anhydrous acetonitrile (1.0–1.2 cm^3), rhodium(II) acetate dimer (1.5 mg, 1 mol%, 3.3 × 10^{-3} mmol), benzyltriethylammonium chloride (15 mg, 20 mol%, 0.066 mmol), benzaldehyde (34 µL, 0.33 mmol) and tosylhydrazone sodium salt **2** (148 mg, 0.50 mmol). The reaction mixture was stirred vigorously at RT for 10 min, then at the required temperature for 40 h. Work up consisted of sequential addition to the reaction mixture of water (0.5 cm^3) and ethyl acetate (0.5 cm^3). The separated aqueous layer was extracted with ethyl acetate (2 × 0.5 cm^3) and the combined extracts dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was analysed by ^{1}H NMR to determine the diastereomeric ratio and then purified by flash column chromatography (ether–hexane 0.5 : 99.5) to afford *trans*-stilbene oxide as a white solid.

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