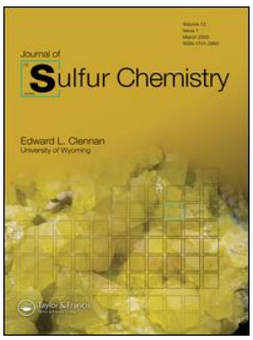

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Synthesis, structure and reactivity of some chiral benzylthio alcohols, 1,3-oxathiolanes and their *S*-oxides

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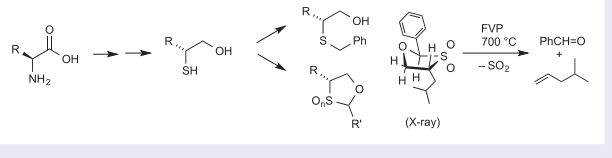
ABSTRACT

A series of amino acid-derived chiral benzylthio alcohols have been prepared and characterized. A chiral mercapto alcohol derived from *S*-leucine has been used to form three chiral 2,4-disubstituted 1,3-oxathiolanes. One of these has been oxidized to the *S*-oxide and another to the *S,S*-dioxide. The *cis* and *trans* isomers have been characterized by ^{1}H NMR in each case and it appears that thermal epimerisation at C-2 is possible at the sulfoxide oxidation state. The X-ray structure of major *trans* diastereomer of 2-phenyl-4-isobutyl-1,3-oxathiolane *S,S*-dioxide shows an envelope conformation with oxygen at the flap and an internal angle at sulfur of just 93.8°. This compound fragments upon flash vacuum pyrolysis at 700°C to give SO_2, benzaldehyde and 4-methylpent-1-ene.



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1,3-oxathiolane; pyrolysis; sulfoxide; sulfone; X-ray structure

1. Introduction

Some time ago we were interested in preparing chiral 1,4,2-oxathiaphosphorinanes as potential chiral acyl anion equivalents. Although a wide range of heterocyclic acyl and formyl anion equivalents have been developed [1], to the best of our knowledge this ring system exemplified by **A** (Figure 1), which is a hybrid between a Wadsworth-Emmons reagent and a 1,3-dithiane, is not known. As shown, we envisaged forming the ring by an intramolecular Arbuzov process on a substrate readily derived from a chiral (benzylthio) alcohol **B**, itself readily accessible in a few conventional steps from an α-amino acid. The related heterocyclic phosphonium salts **C** are known from a single publication [2] but are

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difficult to prepare and have not been exploited synthetically. We recently reported the synthesis, structure and reactivity of some 2-substituted 1,3-oxathiolanes and their *S*-oxides **D** [3]. In this paper we describe the synthesis and characterization of a series of the benzylthio alcohols **B** and also the formation, structure and reactivity of some chiral 2,4-disubstituted 1,3-oxathiolanes and their *S*-oxides **E**. As shown these are also derived via the mercapto alcohol from amino acids.

2. Results and discussion

Our synthesis started by diazotization of the amino acids leucine, valine and isoleucine bearing bulky alkyl side chains in the presence of 3–6 equivalents of potassium bromide [4] to afford the α-bromo acids **1–3** (Scheme 1). These showed good agreement of boiling point and optical rotation with literature values. An attempt was then made to introduce sulfur by addition of potassium ethyl xanthate to a solution of the α-bromo acids in aqueous sodium carbonate. This proved to be highly effective in the case of bromo acid **1** to afford the previously unknown derivative **4** in almost quantitative yield. However, as previously documented [5], the corresponding reaction with the more sterically hindered bromo acids **2** and **3** failed. Direct reduction of the xanthate **4** with lithium aluminium hydride gave a mixture of mercapto alcohol and mercapto acid in both THF and diethyl ether, so the acid group was first converted into the ethyl ester to give **5**, which was then efficiently reduced to afford the mercapto alcohol **6** as an intensely unpleasant smelling oil. To give the first target benzylthio alcohol **7**, this was *S*-benzylated by treatment with sodium ethoxide in ethanol followed by benzyl bromide.

In order to access the full range of target benzylthio alcohols **B** we adopted the more direct approach of initial nucleophilic displacement using sodium benzylthiolate (Scheme 2). Thus the bromo acids **1–3** afforded the benzylthio acids **8–10** in good yield. Of these three compounds, only **9** has been previously reported [6] and it showed good agreement with literature NMR data although, as noted in the experimental section, there is a slight error in the literature interpretation. The three acids were then readily esterified to give the benzylthio esters **11–13** in almost quantitative yield. Again two of these three compounds are previously unknown and only compound **11** is briefly mentioned in the literature [7] with no characterization data. The final reduction to the target benzylthio alcohols **7**, **14**, and **15** was achieved in high yield with lithium aluminium hydride in

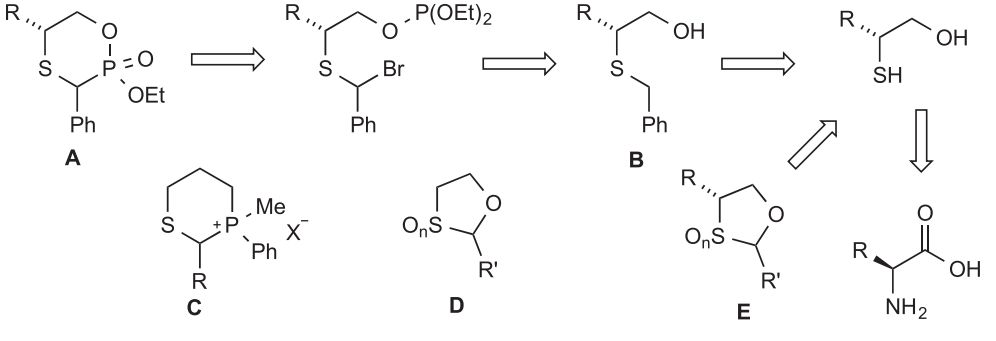
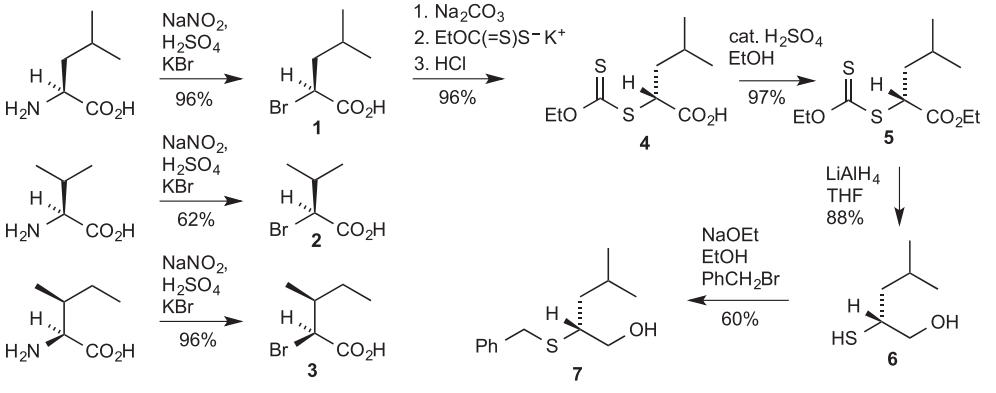
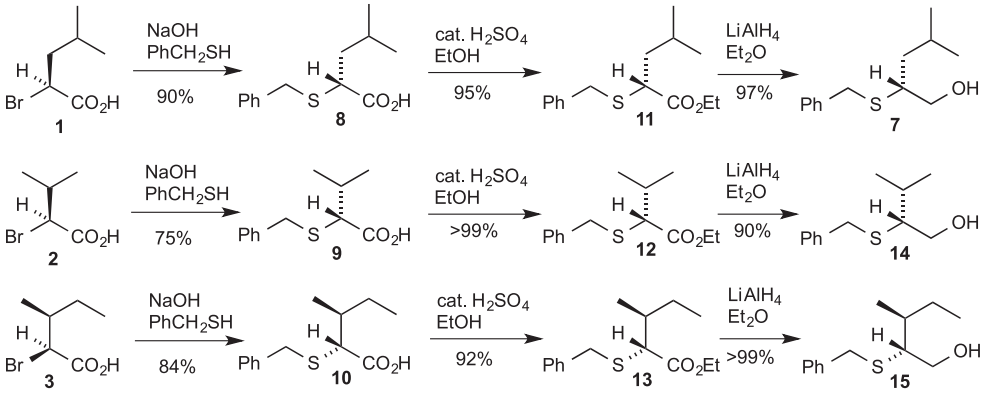


Figure 1. Retrosynthetic analysis of target heterocycles **A** and structure of related compounds.



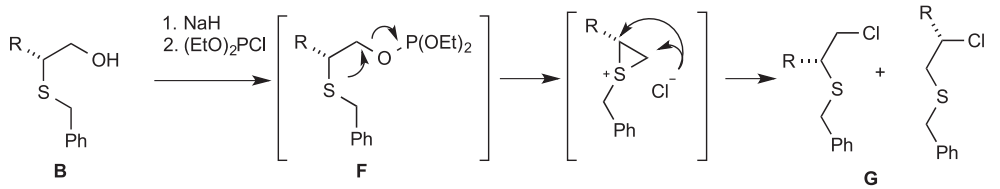
Scheme 1. First approach to benzylthio alcohols.



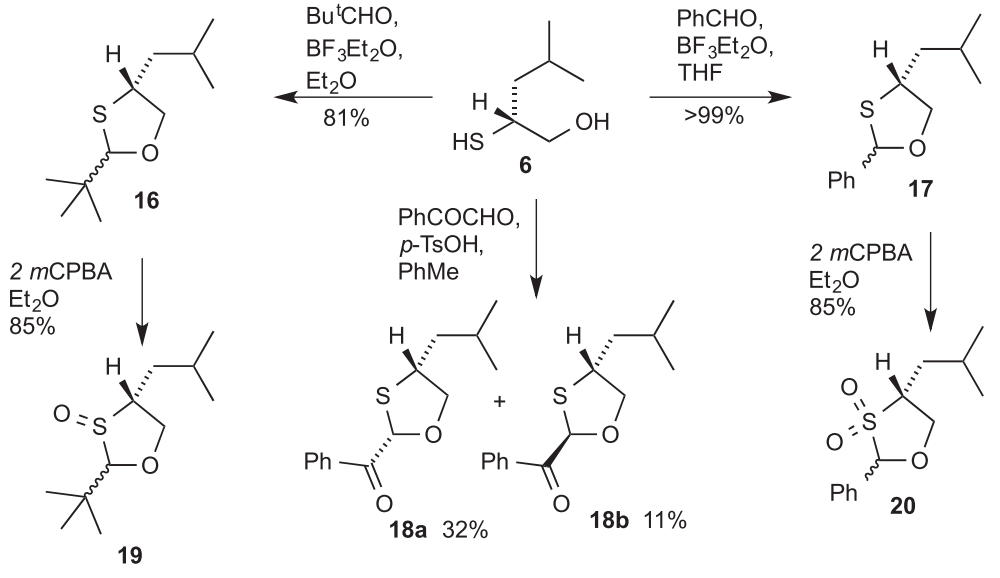
Scheme 2. Second approach to benzylthio alcohols.

diethyl ether. Of these three compounds, the valine-derived example **14** has been reported by Evans [8] and used to form mixed P/S ligands for palladium catalysis. In his study, installation of an additional stereocentre adjacent to OH was followed by reaction with Ar_2PCl to give a phosphinite much as suggested in Figure 1. Importantly however, our optical rotation value for **14** is roughly half that reported by Evans and also for the isoleucine derived compounds **10**, **13** and **15** with a second and presumably invariant stereocentre present, diastereomeric mixtures were evident by NMR, thus pointing to a degree of racemization, most likely at the stage of the initial sodium benzylthiolate substitution. Clearly this problem would need to be addressed for effective implementation of the strategy outlined in Figure 1. However, in the mean time, progress in this direction was halted by the discovery that treatment of the benzylthio alcohols **7**, **14** and **15** with sodium hydride followed by diethyl chlorophosphite gave not the expected phosphites **F** but rather the isomeric chlorides **G** formed via an intermediate thiiranium salt (Scheme 3). This will be described in detail elsewhere.

The chiral mercapto alcohol **6** is a member of a potentially useful but uncommon class of compounds, although it might be noted that there is one paper [9] involving use of the isopropyl analogue derived from (*S*)-valine as a chiral auxiliary. We realized that



Scheme 3. Undesired reactivity of sulfide-containing phosphites.

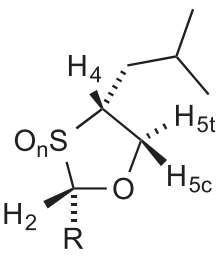


Scheme 4. Preparation and oxidation of 1,3-oxathiolanes.

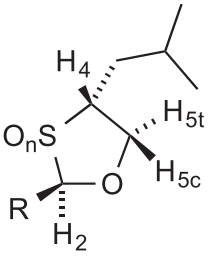
reaction of compound **6** with aldehydes would give a range of chiral 2,4-disubstituted-1,3-oxathiolanes. The stereoselectivity of the ring closure process, leading to *cis* and *trans* isomers, is of interest and, after *S*-oxidation, there is one report of such an (achiral) system acting as a formyl anion equivalent [10]. Substituted 1,3-oxathiolanes have been prepared in a variety of ways including by 1,3-dipolar cycloaddition, either of carbonyl ylides to thioketones [11], or of thiocarbonyl ylides to carbonyl compounds [12,13]. Reaction of compound **6** with pivalaldehyde and benzaldehyde in boiling diethyl ether with addition of boron trifluoride etherate gave the 1,3-oxathiolanes **16** and **17**, respectively, in high yield as inseparable mixtures of diastereomers. In the case of phenylgloxal, reaction with **6** catalysed by *p*-toluenesulfonic acid in toluene gave the diastereomers **18a** and **18b** which were separated by chromatography (Scheme 4).

With a view to developing potential chiral acyl anion equivalents, we attempted to oxidize the oxathiolanes **16** and **17** to the corresponding sulfones. Treatment with two equivalents of *meta*-chloroperbenzoic acid in diethyl ether cleanly gave only mono-oxidation to the sulfoxide **19** in the case of the *tert*-butyl compound **16**, presumably due to steric hindrance, whereas the phenyl compound **17** did undergo full oxidation to the desired sulfone

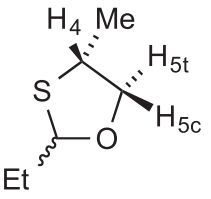
Table 1. Observed ^{1}H NMR chemical shifts (ppm) and coupling contants (Hz) for the *cis* and *trans* 1,3-oxathiolanes **16–20** as well as comparison compound **21** [20].



cis



trans



21

Compd	Ratio	H-2	H-4	H-5c	H-5t	J(4-5t)	J(4-5c)	J(5t-5c)
cis-**16**	66	4.88	3.45	3.78	3.98	2	6	10
trans-**16**	34	4.95	3.44	4.31	3.35	9	6	9.3
cis-**17**	52	6.18	3.91	4.03	4.15	3	4	7
trans-**17**	48	6.12	3.76	4.51	3.61	7	5	7
cis-**18**	75	5.20	4.00	3.66	4.04	3	5	12
trans-**18**	25	5.08	3.98	4.34	3.66	10	4	12
cis-**21**	—	5.04	3.58	3.83	3.89	2.6	5.1	9.1
trans-**21**	—	5.14	3.62	4.27	3.38	8.5	5.6	9.0
cis-**19**	61	4.03	3.12	4.23	4.33	4	0	10
trans-**19**	39	4.03	2.52	4.41	3.84	10	6	10
cis-**20**	13	5.23	3.35	4.32	4.49	6	3	9
trans-**20**	87	5.10	3.35	4.71	3.84	11	8	11

20. The structure of the new oxathiolane compounds **16–20** was now examined by NMR and in the case of **20** X-ray diffraction.

The application of ^{1}H NMR to conformational analysis of substituted 1,3-oxathiolane systems is well established and has been summarized in various review series covering this ring system [14–16]. Early studies on 2-substituted 1,3-oxathiolanes [17,18] were followed by detailed analysis of examples including 2,4-dialkyl systems [19,20] and in later papers the *S*-oxidised systems are also included [21,22]. The data collected for the compounds involved here is presented in Table 1 and conforms to a logical pattern, both in terms of chemical shift and coupling constants. In particular, the fact that the chemical shifts for the two H-5 protons are widely separated for the *trans* isomer and those for H-5 of the *cis* isomer are closer and in fact come between those for *trans*, is fully consistent with the literature pattern for other 2,4-dialkyl-1,3-oxathiolanes [20]. Similarly, the coupling constants between H_4 and H_5 (*cis*) are fairly equal between *cis* and *trans* isomers in each case, but the value of the coupling constant between H_4 and H_5 (*trans*) is much greater for the *trans* isomers (7–11 Hz) than the corresponding *cis* isomers (2–6 Hz), again fully consistent with the literature pattern [20] and in fact this allowed us to confidently assign signals to *cis* and *trans* isomers in the case of **17** where they were present in almost a 1:1 ratio. To illustrate the point, literature data [20] for 2-ethyl-4-methyl-1,3-oxathiolane are included in Table 1 for comparison. When we come to the *S*-oxidised systems **19** and **20**, the same pattern of chemical shifts is observed although the coupling constants are now more unequal for both *cis* and *trans* somers.

Since the enhanced acidity of H-2 expected for the *S,S*-dioxide **20** together with the known propensity of this ring system to fragment thermally with loss of SO_2 and an alkene

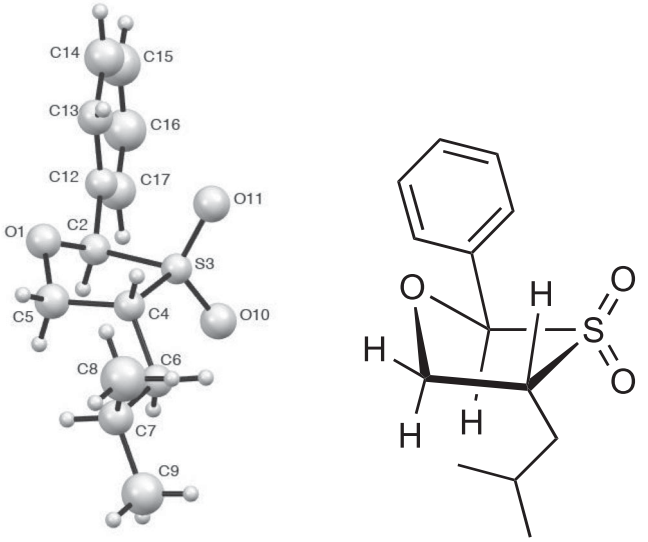


Figure 2. X-Ray structure of *trans*-**20** (ORTEP diagram, 50% probability level). Selected bond lengths and angles: O1-C2 1.404(4), C2-S3 1.822(3), S3-C4 1.818(3), C4-C5 1.510(4), C5-O1 1.454(4) Å; C2-O1-C5 106.9(2), O1-C2-S3 103.3(2), C2-S3-C4 93.8(2), S3-C4-C5 102.6(2), C4-C5-O1 109.2(3)°.

[10] suggested that this compound might act as an effective chiral benzoyl anion equivalent, the relative configuration of the major and minor diastereomers of this compound was clearly of interest. Fortunately the major diastereomer was readily obtained in pure form by recrystallisation from ethyl acetate. A single crystal X-ray diffraction study showed this to be the *trans* isomer (Figure 2) showing an obvious 'envelope' conformation with the ring oxygen out of the plane of the remaining four essentially coplanar ring atoms and a ring angle of only 93.8° at sulfur. The angle between the ring plane and flap of the envelope is 47.8°. This is highly consistent with the structure of 2-benzyl-1,3-oxathiolane *S,S*-dioxide **22** from our previous paper [3] and the only two previous X-ray structures of 1,3-oxathiolane *S,S*-dioxides: the carbohydrate-derived compounds **23** [23,24] and **24** [25] (Figure 3). These all show very similar envelope conformations and the bond lengths and angles within the ring are very similar to those observed for **20**. The values for the C(2)−S and S−C(4) bond lengths as well as the C(2)−S−C(4) angle also agree well with those observed for the few unsaturated 1,3-oxathiole *S,S*-dioxides **25** [26,27] and **26** and **27** [28] to be crystallographically characterized although in all these cases the oxathiolane ring is planar.

The fact that oxidation of the 2-phenyl-1,3-oxathiolane **17** which was a 52:48 mixture of *cis* and *trans* isomers gives the corresponding sulfone **20** as a 13:87 mixture of *cis* and *trans* isomers requires some explanation. Although the isomer ratio of the 2-*tert*-butyl compound **16** was essentially the same as that of the final sample obtained for its *S*-oxide **19**, the behavior of the latter gave a valuable clue as to what may be going on. As described in the experimental section, the oxidation of **16** (66:34 *cis/trans)* initially gave the sulfoxide **19** as a 34:66 *cis/trans* mixture after distillation, but this was progressively transformed upon repeated vacuum distillation first to 55:45 *cis/trans* and finally to a 61:39 *cis/trans* ratio. The fact that thermal epimerisation is possible at the sulfoxide stage may be due to

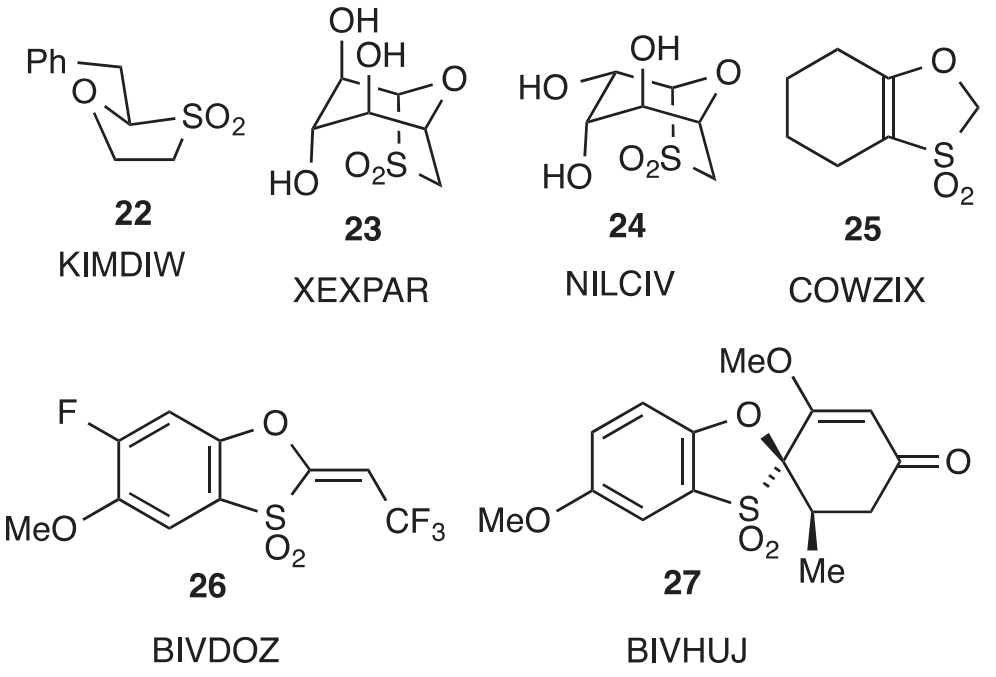
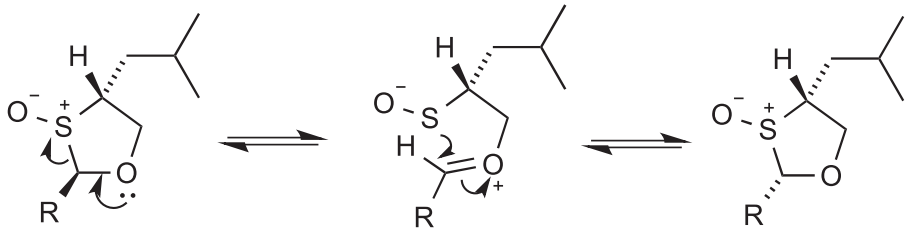


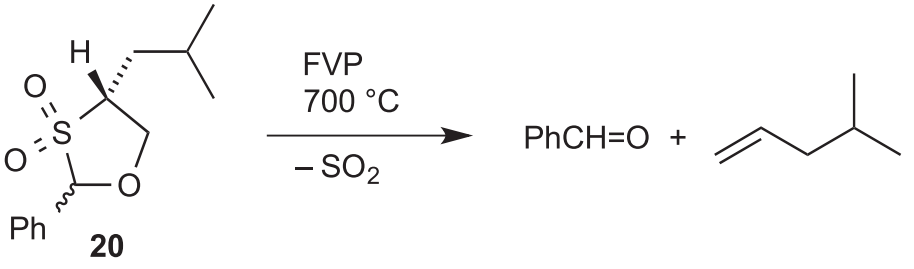
Figure 3. 1,3-Oxathiolane and 1,3-oxathiole *S,S*-dioxides previously characterized by X-ray crystallography with CCDC Reference Codes.



Scheme 5. Possible epimerisation mechanism of 1,3-oxathiolane *S*-oxides.

ring opening and re-closure as shown in Scheme 5 and the occurence of a similar process at the intermediate stage in the oxidation of **17** may explain the dramatic change in the isomer ratio.

We now examined the pyrolysis behavior of the *S,S*-dioxide **20** under flash vacuum pyrolysis (FVP) conditions. Thermal extrusion of SO_2 from five-membered ring heterocycles is well known [29], but we are only aware of two previous reports describing such extrusion from 1,3-oxathiolane 3,3-dioxides. In the first [10] 4,4-dimethyl-1,3-oxathiolane 3,3-dioxide was found to fragment cleanly into SO_2, isobutene and formaldehyde. This allowed Gokel and coworkers to use the compound as a formyl anion equivalent, by deprotonation and alkylation with an alkyl halide, RX, at C-2 followed by thermal fragmentation to generate the corresponding aldehyde RCHO. In our own recent study [3], both 2-benzyl- and 2-benzylidene-1,3-oxathiolane *S,S*-dioxide were found to fragment cleanly with loss of SO_2 and ethene to give, respectively, phenylacetaldehyde and products derived from



Scheme 6. FVP behavior of sulfone **20**.

phenylketene. Consistent with this pattern, FVP of compound **20** resulted in complete reaction at 700°C with loss of SO_2 to afford benzaldehyde (60%) and the expected alkene 4-methylpent-1-ene (78%) (Scheme 6). While there are various mechanistic possibilities for this process, we believe it most likely proceeds by extrusion of benzaldehyde to give 2-isobutylthiirane *S*,*S*-dioxide which rapidly decomposes to the alkene and SO_2. In our previous study [3] significant evidence was obtained for formation of thiirane *S*-oxide by extrusion of phenylacetaldehyde from 2-benzyl-1,3-oxathiolane. Unfortunately conditions have not so far been found for efficient deprotonation and alkylation at C-2 of the sulfone **20** thus frustrating its potential use as a chiral benzoyl anion equivalent.

3. Conclusion

Although the initial objective of developing effective chiral acyl anion equivalents starting from amino acids has not been realized, several new chiral sulfur containing alcohols and derived 1,3-oxathiolanes have been obtained and characterized. The structure of the latter has been studied by ^{1}H NMR of the *cis* and *trans* isomers giving results in good agreement with literature precedent for achiral systems. The first gas phase fragmentation of a chiral 1,3-oxathiolane *S*,*S*-dioxide leading to loss of SO_2 and formation of an aldehyde and an alkene is reported.

4. Experimental section

4.1. General

Melting points were determined on a Reichert hot-stage microscope and are uncorrected. NMR spectra were recorded for ^{1}H at 300 or 200 MHz and for ^{13}C at 75 or 50 MHz on Bruker instruments. Spectra were obtained for solutions in $CDCl_3$ with Me_4Si as internal reference and coupling constants are given in Hz. IR spectra were measured on a Perkin Elmer 1420 spectrophotometer as Nujol mulls for solids and thin films for liquids. Low and high resolution mass spectra were run on an AEI Kratos MS50 spectrometer. Elemental analysis was performed on a Carlo-Erba 1106 elemental analyser. Optical rotations were recorded on an Optical Activity AA1000 digital polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Flash vacuum pyrolysis was conducted using a conventional flow system with the sample being volatilized from an electrically heated inlet tube through a horizontal quartz reactor tube (30 × 2.5 cm) heated externally by a laboratory tube furnace, and connected via a liquid nitrogen-cooled product collection trap to a rotary vacuum pump. The

system was maintained at pressures in the range 10^{-3}–10^{-2} Torr corresponding to a contact time in the hot zone of 1–10 ms. Full details of the procedure are given in a recent publication [30]. CCDC 1861140 (*trans*-**20**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1. Preparation of α-bromo acids **1–3**

These compounds were prepared by modification of the method of Izumiya [4]. To a stirred solution of an α-amino acid (1 eq.) containing potassium bromide (3 eq.) in sulfuric acid (1.5 M) at 0 °C was added sodium nitrite (1.2 eq.) portionwise over a 30 min period maintaining the temp. at or near 0 °C. The resulting solution was stirred for 1 h and then extracted with ethyl acetate (3 × 40 mL). The organic extract was dried and evaporated to give the product which was purified as stated.

a. (*S*)-2-Bromo-4-methylpentanoic acid **1**

Reaction as above using (*S*)-leucine (31.0 g, 240 mmol), sulfuric acid (1.5, 160 mL), potassium bromide (85.6 g, 720 mmol) and sodium nitrite (19.9 g, 288 mmol) afforded the title compound (44.9 g, 96%) as a colourless oil after Kugelrohr distillation, bp (oven temp.) 74–75 °C at 0.04 Torr (lit. [31] bp 94 °C at 0.2–0.4 Torr). $[\alpha]_D^{24}$ –56.3 (c 1.5 in $CHCl_3$) [lit. [32] $[\alpha]_D^{24}$ –56.1 (c 1.2 in $CHCl_3$)]. ν_{max}/cm^{-1} 3500–2400, 1710. ^{1}H NMR (300 MHz): 9.75 (1 H, br s, CO_2H), 4.30 (1 H, t, *J* 7, CHBr), 1.93 (2 H, t, *J* 7, CH_2), 1.82 (1 H, m, C*H*Me$_2$), 0.97 (3 H, d, *J* 7, CH*Me*), 0.93 (3 H, d, *J* 7, CH*Me*). ^{13}C NMR (75 MHz): 176.6 (C=O), 44.0 (CHBr), 43.2 (CH_2), 26.3 (CHMe$_2$), 22.3, 21.5 (Me).

b. (*S*)-2-Bromo-3-methylbutanoic acid **2**

Reaction as above using (*S*)-valine (10.0 g, 90 mmol), sulfuric acid (1.5, 100 mL), potassium bromide (64.3 g, 540 mmol) and sodium nitrite (8.2 g, 120 mmol) afforded the title compound (10.1 g, 62%) as a colourless oil after Kugelrohr distillation, bp (oven temp.) 86 °C at 0.04 Torr (lit. [33] bp 119–120 °C at 14 Torr), or low melting crystals mp 41–42 °C (hexane). $[\alpha]_D^{24}$ –20.8 (c 1.2 in Et_2O) [lit. [34] $[\alpha]_D^{24}$ –16.7 (c 5 in 1 M NaOH)]. ν_{max}/cm^{-1} 3600–2400, 1705. ^{1}H NMR (300 MHz): 11.20 (1 H, br s, CO_2H), 4.09 (1 H, d, *J* 7, CHBr), 2.26 (1 H, m, C*H*Me$_2$), 1.12 (3 H, d, *J* 7, CH*Me*), 1.08 (3 H, d, *J* 7, CH*Me*). ^{13}C NMR (75 MHz): 176.1 (C=O), 54.1 (CHBr), 32.2 (*C*HMe$_2$), 20.2, 19.8 (Me).

c. (*S,S*)-2-Bromo-3-methylpentanoic acid **3**

Reaction as above using (*S,S*)-isoleucine (50.0 g, 380 mmol) in sulfuric acid (1.5, 200 mL) containing potassium bromide (135.7 g, 1.1 mol) and sodium nitrite (36.8 g, 530 mmol) afforded the title compound (44.9 g, 96%) as a colourless oil after Kugelrohr distillation, bp (oven temp.) 80 °C at 0.1 Torr (lit. [35] bp 93–95 °C at 1.0 Torr); $[\alpha]_D^{24}$ +10.4 (c 1.5 in MeOH) [lit. [36] $[\alpha]_D^{27}$ +9.3 (MeOH)]; ν_{max}/cm^{-1} 3600–2400, 1700. ^{1}H NMR (300 MHz): 9.50 (1 H, br s, CO_2H), 4.13 (1 H, d, *J* 7, CHBr), 1.75 (1 H, m, C*H*CH$_2$Me), 1.34 (2 H, m, C*H*$_2$Me), 1.06 (3 H, d, *J* 7, CH*Me*), 0.92 (3 H, t, *J* 7, CH$_2$*Me*). ^{13}C NMR (75 MHz): 175.3 (C=O), 52.6 (CHBr), 38.1 (*C*HMe), 26.2 (CH_2), 16.2 (CH*Me*), 10.5 (CH$_2$*Me*).

2. Preparation of potassium *O*-ethyl dithiocarbonate

A solution of potassium ethoxide was prepared by dissolving KOH (42.0 g, 0.75 mol) in dry ethanol (150 mL) and heating the resulting mixture under reflux for 1 h. After cooling, the solution was filtered. The filtrate was cooled in an ice bath and carbon disulfide (45 mL, 0.75 mol) was added dropwise with constant shaking of the reaction flask.

The solid formed was filtered off and washed with ether (3 × 25 mL) to afford potassium *O*-ethyldithiocarbonate (potassium ethyl xanthate) (80.0 g, 76%) as colourless crystals, mp > 200 °C (dec.) [lit. [37] mp 190 °C (dec.)] which were recrystallised from ethanol.

3. Preparation of (*R*)-2-Ethoxythiocarbonylthio-4-methylpentanoic acid **4**

Following the method of Levene [38], a stirred solution of (*S*)-2-bromo-4-methylpentanoic acid **1** (16.0 g, 82 mmol) in water (70 mL) at 0 °C was neutralized by addition of sodium carbonate (8.7 g, 82 mmol) which was followed by addition of potassium *O*-ethyl dithiocarbonate (13.1 g, 82 mmol). This solution was maintained at 0 °C for 8 h and then acidified with cold concentrated hydrochloric acid (11 mL). The mixture was extracted with ether (3 × 40 mL) and the combined extracts washed with brine (2 × 15 mL), dried and evaporated. Kugelrohr distillation afforded the title compound (18.6 g, 96%) as a clear light yellow oil after Kugelrohr distillation, bp (oven temp.) 130 °C at 0.3 Torr (Found: C, 45.98; H, 6.88. $C_9H_{16}O_3S_2$ requires C, 45.74; H, 6.82%). HRMS (EI) *m/z* calcd for $C_9H_{17}O_3S_2$: 237.0619, found: 237.0628 [M + H]. $[\alpha]_D^{22}$ +65.3 (c 1.1 in CH_2Cl_2). ν_{max}/cm^{-1} 3500–2400, 1700. ^{1}H NMR (300 MHz): 9.00 (1 H, br s, CO_2H), 4.67 (2 H, q, *J* 7, CH_2), 4.43 (1 H, t, *J* 7, SCH), 1.80 (1 H, m, $CHMe_2$), 1.70 (2 H, m, CH_2CH), 1.44 (3 H, t, *J* 7, CH_2Me), 1.00 (3 H, d, *J* 7, CHMe), 0.95 (3 H, d, *J* 7, CHMe). ^{13}C NMR (75 MHz): 211.6 (C=S), 177.8 (C=O), 70.8 (OCH_2), 50.4 (CHS), 39.4 (CH_2), 26.1 ($CHMe_2$), 22.3, 22.2 (CHMe), 13.6 (CH_2Me). *m/z* (CI) 237 (M + H^+, 100%), 133 (28), 123(86), 117 (63).

4. Preparation of (*R*)-Ethyl 2-ethoxythiocarbonylthio-4-methylpentanoate **5**

A solution of (*R*)-2-ethoxythiocarbonylthio-4-methylpentanoic acid **4** (14.1 g, 100 mmol) in ethanol (70 mL) containing concentrated sulfuric acid (0.2 mL) was heated under reflux for 6.5 h. After cooling, the solution was partly evaporated. Water (50 mL) was added and the mixture extracted with ether (2 × 50 mL), which was dried and evaporated to give the product. Kugelrohr distillation afforded the title compound (15.3 g, 97%) as a light yellow liquid, bp (oven temp.) 140 °C at 2.0 Torr (Found: C, 50.21; H, 7.35. $C_{11}H_{20}O_3S_2$ requires C, 49.97; H, 7.62%); $[\alpha]_D^{25}$ +59.5 (c 1.4 in CH_2Cl_2). ν_{max}/cm^{-1} 1700. ^{1}H NMR (300 MHz): 4.62 (2 H, q, *J* 7, $MeCH_2OCS_2$), 4.35 (1 H, t, *J* 7, CHS), 4.19 (2 H, q, *J* 7, CO_2CH_2), 1.75 (1 H, m, $CHMe_2$), 1.71 (2 H, m, CH_2CH), 1.41 (3 H, t, J 7, $MeCH_2OCS_2$), 1.27 (3 H, t, J 7, CO_2CH_2Me), 0.97 (3 H, d, J 7, CHMe), 0.93 (3 H, d, J 7, CHMe). ^{13}C NMR (75 MHz): 212.4 (C=S), 171.5 (C=O), 70.3 (OCH_2), 61.6 (OCH_2), 50.8 (CHS), 40.1 (CH_2), 26.2 (CH), 22.3, 22.2 (CHMe), 14.1, 13.6 (CH_2Me). *m/z* (EI) 265 (M + H^+, 17%), 219 (18), 143 (100), 133 (16), 120 (20), 115 (60), 101 (38), 87 (24), 69 (48).

5. Preparation of (*R*)-2-Mercapto-4-methylpentan-1-ol **6**

A solution of (*R*)-ethyl 2-ethoxythiocarbonylthio-4-methylpentanoate **5** (8.7 g, 33 mmol) in dry THF (50 mL) was added dropwise with stirring over a 1 h period to a suspension of lithium aluminium hydride (1.8 g, 49 mmol) in dry THF (50 mL) under nitrogen and the resulting mixture was heated under reflux for 7 h. After cooling, acetone (30 mL) was added to destroy the excess reagent followed by the addition of sulfuric acid (1.5, 40 mL). The THF layer was separated and the product extracted from it with potassium hydroxide (10%, 3 × 40 mL). The combined alkali extracts were acidified with hydrochloric acid (2 M) and the mixture extracted with ether (4 × 25 mL). The combined ether extracts were washed with water (4 × 15 mL), dried and evaporated to afford the title compound (3.9 g, 88%) as a colourless foul smelling liquid after Kugelrohr distillation, bp (oven temp.) 50 °C at 0.1 Torr (Found: C, 53.38; H, 10.46. $C_6H_{14}OS$ requires C, 53.69;

H, 10.51%). HRMS (EI) *m/z* calcd for $C_6H_{14}OS$: 134.0765, found: 134.0762 [M]. $[\alpha]_D^{17}$ +31.0 (c 1.1 in CH_2Cl_2). ν_{max}/cm^{-1} 3600–3100. ^1H NMR (300 MHz): 3.68 (1 H, half AB pattern of d, *J* 11, 5, C*H*$_2$OH), 3.41 (1 H, half AB pattern of d, *J* 11, 7, C*H*$_2$OH), 2.94 (1 H, m, CHS), 2.64 (1 H, br s, OH), 1.86 (1 H, m, C*H*Me$_2$), 1.39 (2 H, m, C*H*$_2$CH), 1.30 (1 H, d, *J* 7, SH), 0.91 (3 H, d, *J* 7, CH*Me*), 0.87 (3 H, d, *J* 7, CH*Me*). ^{13}C NMR (75 MHz): 68.3 (OCH_2), 43.8 (CH_2), 42.1 (CHS), 25.4 (CH), 23.0, 21.6 (Me). *m/z* (EI) 134 (M^+, 5%), 115 (5), 103 (22), 100 (24), 83 (47), 69 (100), 61 (50), 57 (51), 43 (74).

6. Preparation of (*R*)-2-Benzylthio-4-methylpentan-1-ol **7**

A solution of (*R*)-2-mercapto-4-methylpentan-1-ol **6** (8.5 g, 63 mmol) in ethanol (25 mL) was slowly added to a solution of sodium ethoxide (70 mmol) in ethanol (50 mL). After stirring for 15 min, benzyl bromide (12.0 g, 8.3 mL, 70 mmol) was added, dropwise, and after 1 h at RT the mixture was filtered to remove the precipitate of sodium bromide and then evaporated. The residue was dissolved in water (30 mL) and the mixture extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (30 mL), dried and evaporated to give the crude product. Kugelrohr distillation afforded the title compound (6.0 g, 60%) as a pale yellow oil, bp (oven temp.) 175 °C at 0.5 Torr (Found: C, 69.85; H, 9.18. $C_{13}H_{20}OS$ requires C, 69.59; H, 8.99%). HRMS (EI) *m/z* calcd for $C_{13}H_{20}OS$: 224.1235, found: 224.1239 [M]. $[\alpha]_D^{25}$ +50.1 (c 1.2 in CH_2Cl_2). ν_{max}/cm^{-1} 3600–3100. ^1H NMR (200 MHz): 7.4–7.2 (5 H, m, Ph), 3.71 (2 H, s, PhC*H*$_2$S), 3.64 (1 H, half AB pattern of d, *J* 11, 5, C*H*$_2$OH), 3.45 (1 H, half AB pattern of d, *J* 11, 7, C*H*$_2$OH), 2.75 (1 H, m, CHS), 2.07 (1 H, br s, OH), 1.76 (1 H, m, C*H*Me$_2$), 1.38 (2 H, m, C*H*$_2$CH), 0.86 (3 H, d, *J* 7, CH*Me*), 0.76 (3 H, d, *J* 7, CH*Me*). ^{13}C NMR (50 MHz): 138.3 (Ph-C1), 128.8 (Ph, 2CH), 128.6 (Ph, 2CH), 127.1 (Ph-C4), 64.0 (OCH_2), 46.6 (CHS), 40.5 (CH_2), 34.5 (CH_2S), 25.2 (CH), 22.9, 21.9 (Me); *m/z* (EI) 224 (M^+, 41%), 193 (43), 137 (51), 123 (14), 91 (100), 65 (16).

7. Preparation of α-benzylthio acids **8–10**

To a stirred solution of the α-bromo acid (1 eq.) containing sodium hydroxide (1 eq.) in water, was added dropwise, a solution of benzyl mercaptan (1 eq.) and sodium hydroxide (1 eq.) in water (50 mL). The resulting mixture was heated under reflux for 7 h. After cooling, the solution was washed with ether (20 mL) and this extract discarded. The aqueous phase was acidified with hydrochloric acid (2 M) and then extracted with ether (3 × 50 mL). The combined organic extracts were dried and evaporated and the products purified as stated.

a. (*R*)-2-Benzylthio-4-methylpentanoic acid **8**

Reaction as above using (*S*)-2-bromo-4-methylpentanoic acid **1** (19.6 g, 100 mmol) and sodium hydroxide (4.0 g, 100 mmol) in water (50 mL) and benzyl mercaptan (12.4 g, 11.7 mL, 100 mmol) and sodium hydroxide (4.0 g, 100 mmol) in water (50 mL) afforded the title compound (21.4 g, 90%) as a clear colourless liquid after removal of the α-hydroxyalcohol by Kugelrohr distillation (Found: C, 65.47; H, 7.87. $C_{13}H_{18}O_2S$ requires C, 65.51; H, 7.61%). HRMS (EI) *m/z* calcd for $C_{13}H_{18}O_2S$: 238.1028, found: 238.1022 [M]. $[\alpha]_D^{22}$ +170.5 (c 1.4 in CH_2Cl_2). ν_{max}/cm^{-1} 3400–2400, 1705. ^1H NMR (200 MHz): 11.18 (1 H, br s, CO_2H), 7.4–7.2 (5 H, m, Ph), 3.90 and 3.82 (2 H, AB pattern, *J* 14, PhC*H*$_2$S), 3.19 (1 H, t, *J* 7, CHS), 1.70 (2 H, m, C*H*$_2$CH), 1.50 (1 H, m, C*H*Me$_2$), 0.83 (3 H, d, *J* 7, CH*Me*), 0.71 (3 H, d, *J* 7, CH*Me*). ^{13}C NMR (50 MHz): 180.0 (C=O), 137.5 (Ph-C1), 129.4 (Ph, 2CH), 128.7 (Ph, 2CH), 127.5 (Ph-C4), 43.7 (CHS), 39.5 (CH_2), 36.3 (CH_2S), 25.9

(CH), 22.5 (Me), 22.1 (Me). *m/z* (EI) 238 (M^+, 29%), 123 (100), 113 (11), 91 (100), 65 (22), 45 (25).

b. (*R*)-2-Benzylthio-3-methylbutanoic acid **9**

Reaction as above using (*S*)-2-bromo-3-methylbutanoic acid **2** (19.4 g, 110 mmol) and sodium hydroxide (4.3 g, 110 mmol) in water (50 mL) and benzyl mercaptan (13.3 g, 12.5 mL, 110 mmol) and sodium hydroxide (4.3 g, 110 mmol) in water (50 mL) afforded the title compound (18.5 g, 75%) as a clear colourless liquid after Kugelrohr distillation, bp 135 °C at 2.5 Torr (Found: C, 63.84; H, 7.46%. $C_{12}H_{16}O_2S$ requires C, 64.25; H, 7.19%). HRMS (EI) *m/z* calcd for $C_{12}H_{16}O_2S$: 224.0871, found: 224.0866 [M]. $[\alpha]_D^{22}$ +67.7 (c 1.2 in CH_2Cl_2). ν_{max}/cm^{-1} 3500–2400, 1680. ^1H NMR (200 MHz): 9.00 (1 H, br s, CO_2H), 7.40–7.20 (5 H, m, Ph), 3.86 (2 H, s, PhCH_2S), 2.92 (1 H, d, *J* 7, SCH), 2.08 (1 H, m, C*H*Me_2), 1.02 (3 H, d, *J* 7, CH*Me*), 1.00 (3 H, d, *J* 7, CH*Me*) [good agreement with lit. [6] except that there the 4 signals constituting the two Me doublets have been mis-paired to give a false coupling constant of 2.9 Hz]. ^{13}C NMR (50 MHz): 179.0 (C=O), 137.4 (Ph-C1), 129.3 (Ph, 2CH), 128.6 (Ph, 2CH), 127.4 (Ph-C4), 53.6 (CHS), 36.2 (CH_2S), 29.3 (CH), 20.7 (Me), 19.8 (Me) [good agreement with lit. [6]]. *m/z* (EI) 224 (M^+, 33%), 179 (3), 140 (30), 138 (29), 123 (100), 91 (100), 76 (52) 73 (48), 43 (35).

c. (3*S*)-2-Benzylthio-3-methylpentanoic acid **10**

Reaction as above using (*S,S*)-2-bromo-3-methylpentanoic acid **3** (37.7 g, 193 mmol) and sodium hydroxide (7.7 g, 193 mmol) in water (75 mL) and benzyl mercaptan (24.0 g, 22.7 mL, 193 mmol) and sodium hydroxide (7.7 g, 193 mmol) in water (75 mL), followed by distillation using a Vigreux column afforded the title compound (38.5 g, 84%), as a 54: 46 mixture of 2 diastereomers, as a clear colourless liquid, bp 170 °C at 2.0 Torr (Found: C, 65.49; H, 7.98. $C_{13}H_{18}O_2S$ requires C, 65.51; H, 7.61%). HRMS (EI) *m/z* calcd for $C_{13}H_{18}O_2S$: 238.1028, found: 238.1027 [M]. ν_{max}/cm^{-1} 3600–2300, 1705. ^1H NMR (300 MHz): 10.35 (1 H, br s, CO_2H), 7.32 (5 H, m, Ph), 3.88 and 3.78 (2 H, AB pattern, *J* 14, PhCH_2S), 3.01 and 2.99 (1 H, d, J 7, CHS), 1.86 and 1.72 (1 H, m, C*H*CH_2), 1.40 and 1.20 (2 H, m, CH_2Me), 1.00 (3 H, d, *J*, C*H*Me), 0.80 and 0.79 (3 H, t, *J* 7, CH_2*Me*). ^{13}C NMR (75 MHz): major diastereomer 179.4 (C=O), 137.5 (Ph-C1), 129.4 (Ph, 2CH), 128.6 (Ph, 2CH), 127.4 (Ph-C4), 51.9 (CHS), 36.1 (CH_2S), 35.6 (CH), 27.4 (CH_2), 16.1 (Me), 11.3 (Me); minor diastereomer 179.1 (C=O), 137.5 (Ph-C1), 129.3 (Ph, 2CH), 128.6 (Ph, 2CH), 127.4 (Ph-C4), 52.0 (CHS), 36.2 (CH_2S), 35.3 (CH), 26.0 (CH_2), 16.8 (Me), 10.5 (Me). *m/z* (EI) 238 (M^+, 10%), 123 (100), 91 (87), 65 (9).

8. Preparation of α-benzylthio esters **11–13**

A stirred solution of an α-benzylthio acid (1 eq.) in excess ethanol containing sulfuric acid (0.5 mL) was heated under reflux for 6.5 h. After cooling, the excess ethanol was removed at the water pump. Water (50 mL) was added and the mixture extracted with ether (4 × 40 mL). The ether extracts were washed with a saturated solution of sodium bicarbonate (2 × 30 mL), dried and evaporated to give the product which was purified as stated.

a. (*R*)-Ethyl 2-benzylthio-4-methylpentanoate **11**

Reaction as above using (*R*)-2-benzylthio-4-methylpentanoic acid **8** (25.0 g, 105 mmol) and ethanol (100 mL) afforded the title compound (26.5 g, 95%) as a light yellow liquid after Kugelrohr distillation, bp (oven temp.) 150 °C at 2.0 Torr (Found: C, 67.56; H,

8.16. $C_{15}H_{22}O_2S$ requires C, 67.63; H, 8.32%). HRMS (EI) *m/z* calcd for $C_{15}H_{22}O_2S$: 266.1341, found: 266.1348 [M]. $[\alpha]_D^{22}$ +144.4 (c 1.1 in CH_2Cl_2). ν_{max}/cm^{-1} 1725. ^1H NMR (300 MHz): 7.40–7.25 (5 H, m, Ph), 4.16 (2 H, q, *J* 7, C*H*$_2$Me), 3.82 and 3.77 (2 H, AB pattern, *J* 13, PhC*H*$_2$S), 3.20 (1 H, t, *J* 7, CHS), 1.77–1.44 (3 H, m, C*H*$_2$C*H*), 1.28 (3 H, t, *J* 7, CH$_2$*Me*), 0.83 (3 H, d, *J* 7, CH*Me*), 0.74 (3 H, d, J 7, CH*Me*). ^{13}C NMR (75 MHz): 173.1 (C=O), 137.8 (Ph-C1), 129.2 (Ph, 2CH), 128.6 (Ph, 2CH), 127.2 (Ph-C4), 61.0 (OCH_2), 44.2 (CHS), 39.8 (CH_2), 35.8 (CH_2S), 25.9 (CH), 22.3 (Me), 22.0 (Me), 14.2 (Me). *m/z* (EI) 266 (M^+, 33%), 210 (7), 193 (9), 144 (57), 137 (16), 123 (64), 101 (76), 91 (100), 73 (18), 65 (20).

b. (*R*)-Ethyl 2-benzylthio-3-methylbutanoate **12**

Reaction as above using (R)-2-benzylthio-3-methylbutanoic acid **9** (13.0 g, 60 mmol) and ethanol (50 mL) afforded the title compound (15.1 g, 100%) as a colourless liquid after Kugelrohr distillation, bp (oven temp.) 150 °C at 4.0 Torr (Found: C, 67.11; H, 8.26%. $C_{14}H_{20}O_2S$ requires C, 66.63; H, 7.99%). HRMS (EI) *m/z* calcd for $C_{14}H_{20}O_2S$: 252.1184, found: 252.1191 [M]. $[\alpha]_D^{24}$ +55.3 (c 1.3 in CH_2Cl_2). ν_{max}/cm^{-1} 1720. ^1H NMR (300 MHz): 7.40–7.25 (5 H, m, Ph), 4.19 (2 H, q, *J* 7, CH_2Me), 3.79 (2 H, s, PhC*H*$_2$S), 2.90 (1 H, d, *J* 11, CHS), 2.06 (1 H, m, C*H*Me$_2$), 1.29 (3 H, t, *J* 7, CH$_2$*Me*), 1.00 (3 H, d, *J* 7, CH*Me*), 0.95 (3 H, d, *J* 7, CH*Me*). ^{13}C NMR (75 MHz): 172.7 (C=O), 137.8 (Ph-C1), 129.2 (Ph, 2CH), 128.6 (Ph, 2CH), 127.3 (Ph-C4), 60.9 (OCH_2), 54.2(CHS), 36.0 (CH_2S), 29.6 (CH), 20.7 (Me), 20.0 (Me), 14.2 (CH_2Me). *m/z* (EI) 252 (M^+, 41%), 179 (30), 130 (57), 123 (67), 91 (100), 65 (20).

c. (3*S*)-Ethyl 2-benzylthio-3-methylpentanoate **13**

Reaction as above using (3*S*)-2-benzylthio-3-methylpentanoic acid **10** (25.5 g, 110 mmol) and ethanol (60 mL) afforded the title compound (26.2 g, 92%), as a 65:35 mixture of diastereomers, as a colourless liquid after Kugelrohr distillation, bp (oven temp.) 130 °C at 2.0 Torr (Found: C, 67.32; H, 8.50. $C_{15}H_{22}O_2S$ requires C, 67.63; H, 8.32%). ν_{max}/cm^{-1} 1720. major diastereomer ^1H NMR (300 MHz): 7.40–7.25 (5 H, m, Ph), 4.18 (2 H, q, *J* 7, CH_2Me), 3.78 (2 H, s, $PhCH_2S$), 3.02 (1 H, d, *J* 7, CHS), 1.86 (1 H, m, $CHCH_2$), 1.28 (3 H, t, *J* 7, CH_2Me), 1.18 (2 H, m, CH_2Me), 0.98 (3 H, d, *J* 7, CHMe), 0.81 (3 H, t, *J* 7, CH_2Me). ^{13}C NMR (75 MHz): 172.9 (C=O), 137.8 (Ph-C1), 129.3 (Ph, 2CH), 128.6 (Ph, 2CH), 127.3 (Ph-C4), 60.9 (CH_2), 52.6 (CHS), 35.9 (CH_2S), 35.8 (CH), 27.4 (CH_2), 16.3 (Me), 14.2 (Me), 11.3 (Me); minor diastereomer ^1H NMR (300 MHz): 7.40–7.25 (5 H, m, Ph), 4.18 (2 H, q, *J* 7, CH_2Me), 3.77 (2 H, s, $PhCH_2S$), 3.01(1 H, d, *J* 7, CHS), 1.66 (1 H, m, $CHCH_2$), 1.42 (2 H, m, CH_2Me), 1.28 (3 H, t, *J* 7, CH_2Me), 0.93 (3 H, d, *J* 7, CHMe), 0.78 (3 H, t, *J* 7, CH_2Me). ^{13}C NMR (75 MHz): 172.7 (C=O), 137.8 (Ph-C1), 129.3 (Ph, 2CH), 128.6 (Ph, 2CH), 127.3 (Ph-C4), 60.9 (CH_2), 52.4 (CHS), 36.0 (CH_2S), 35.6 (CH), 26.1 (CH_2), 16.8 (Me) 14.2 (Me), 10.5 (Me). *m/z* (EI) 266 (M^+, 49%), 193 (14), 144 (57), 123 (59), 115 (86), 91 (100).

9. Preparation of α-benzylthio alcohols from the esters

A solution of an α-benzylthio ester (1 eq.) in dry ether was added to a suspension of excess lithium aluminium hydride in dry ether under nitrogen and the resulting mixture heated under reflux for 3 h. After cooling, acetone was added to destroy the excess reagent followed by the addition of sulfuric acid. The mixture was extracted with ether which was separated, dried and evaporated to give the product which was purified as stated.

a. (*R*)-2-Benzylthio-4-methylpentan-1-ol **7**

Reaction was carried out as above using (R)-ethyl 2-benzylthio-4-methylpentanoate **11** (17.0 g, 103 mmol) and dry ether (50 mL) and lithium aluminium hydride (4.9 g, 130 mmol) in dry ether (140 mL). After cooling, acetone (50 mL) and sulfuric acid (1.5 M, 60 mL) were added. Kugelrohr distillation afforded the title compound (13.9 g, 97%) as a colourless liquid, bp (oven temp.) 135 °C at 0.2 Torr; $[\alpha]_D^{25}$ +52.5 (c 1.4 in CH_2Cl_2); For further characterization see 6.

b. (*R*)-2-Benzylthio-3-methylbutan-1-ol **14**

Reaction was carried out as above using (R)-ethyl 2-benzylthio-3-methylbutanoate **12** (8.0 g, 32 mmol) in dry ether (20 mL) and lithium aluminium hydride (1.4 g, 36 mmol) in dry ether (100 mL). After cooling, acetone (50 mL) and sulfuric acid (1.5 M, 60 mL) were added. Kugelrohr distillation afforded the title compound (6.0 g, 90%) as a colourless liquid, bp (oven temp.) 120 °C at 0.2 Torr (Found: C, 68.33; H, 8.94%. $C_{12}H_{18}OS$ requires C, 68.52; H, 8.63%). HRMS (EI) *m/z* calcd for $C_{12}H_{18}OS$: 210.1078, found: 210.1087 [M]. $[\alpha]_D^{22}$ +11.6 (c 1.2 in CH_2Cl_2) [lit. [8] $[\alpha]_D^{23}$ +22.9 (c 0.93 in CH_2Cl_2)]. ν_{max}/cm^{-1} 3600–3100. ^{1}H NMR (300 MHz): 7.40–7.25 (5 H, m, Ph), 3.76 and 3.72 (1 H, AB pattern, *J* 13, PhCH_2S), 3.68 (1 H, half AB pattern of d, *J* 12, 4, CH_2OH), 3.51 (1 H, half AB pattern of d, *J* 12, 8, CH_2OH), 2.53 (1 H, d of t, *J* 8, 5, CHS), 2.09 (1 H, br s, OH), 1.89 (1 H, m, $CHMe_2$), 0.95 (6 H, d, *J* 7, $CHMe_2$) [good agreement with lit. [8]]. ^{13}C NMR (75 MHz): 138.5 (Ph-C1), 128.9 (Ph-C4), 128.6 (Ph, 2CH), 127.1 (Ph, 2CH), 62.8 (OCH_2), 56.2 (CHS), 36.4 (CH_2S), 29.8 (CH), 20.4 (Me), 19.5 (Me) [good agreement with lit. [8]]. *m/z* (EI) 210 (M^+, 25%), 179 (33), 145 (12), 123 (16), 91 (100), 65 (19).

c. (*R*)-2-Benzylthio-3-methylpentan-1-ol **15**

Reaction was carried out as above using (*R*)-ethyl 2-benzylthio-3-methylpentanoate **13** (6.0 g, 23 mmol) in dry ether (20 mL) and lithium aluminium hydride (0.9 g, 24 mmol) in dry ether (80 mL). After cooling, acetone (30 mL) and sulfuric acid (1.5 M, 50 mL) were added. The ether layer was separated, dried and evaporated to give the title compound (5.0 g, 100%) as a 74:26 mixture of diastereomers as a colourless liquid (Found: C, 69.84; H, 9.06. $C_{13}H_{20}OS$ requires C, 69.59; H, 8.99%). ν_{max}/cm^{-1} 3500–3050. major diastereomer ^{1}H NMR (300 MHz): 7.40–7.25 (5 H, m, Ph), 3.72 (2 H, s, $PhCH_2S$), 3.66 (1 H, half AB pattern of d, *J* 12, 4, CH_2OH), 3.52 (1 H, half AB pattern of d, *J* 12, 8, CH_2OH), 2.55 (1 H, d of t, *J* 8, 5, CHS), 2.35 (1 H, br s, OH), 1.66 (1 H, m, C*H*Me), 1.20 (2 H, m, CH_2Me), 0.90 (3 H, d, *J* 7, CH*Me*), 0.80 (3 H, t, *J* 7, CH_2*Me*). ^{13}C NMR (75 MHz): 138.3 (Ph-C1), 128.8 (Ph-C2,C6), 128.4 (Ph-C3,C5), 127.0 (Ph-C4), 63.4 (CH_2), 54.5 (CHS), 36.6 (CH), 36.4 (CH_2S), 27.0 (CH_2), 16.2 (Me), 11.6 (Me); minor diastereomer ^{1}H NMR (300 MHz): 7.40–7.25 (5 H, m, Ph), 3.72 (2 H, s, PhCH_2S), 3.64 (1 H, half AB pattern of d, *J* 12, 4, CH_2OH), 3.50 (1 H, half AB pattern of d, *J* 12, 8, CH_2OH), 2.52 (1 H, d of t, *J* 8, 5, CHS), 2.35 (1 H, br s, OH), 1.42 (1 H, m, C*H*Me), 1.22 (2 H, m, CH_2Me), 0.88 (3 H, d, J 7, CH*Me*), 0.79 (3 H, t, J 7, CH_2*Me*). ^{13}C NMR (75 MHz): 138.5 (Ph-C1), 128.8 (Ph, 2CH), 128.4 (Ph, 2CH), 127.0 (Ph-C4), 62.0 (CH_2), 53.8 (CHS), 36.2 (CH_2S), 36.1 (CH), 26.3 (CH_2), 15.6 (Me), 11.6 (Me). *m/z* (EI) 224 (M^+, 35%), 193 (40), 137 (15), 122 (28), 91 (100).

10. Preparation of chiral 1,3-oxathiolanes

To a stirred boiling solution of the mercapto alcohol (1 eq.) containing an aldehyde (1 eq.) in dry ether or THF was added dropwise over 1 h boron trifluoride diethyl etherate (1 eq.) in dry ether or THF. This solution was heated for the time stated after addition was

complete. The cooled solution was then washed twice with sodium bicarbonate (0.1 M, 2 × 15 mL) and with a saturated brine solution (2 × 20 mL). The organic extract was then dried and evaporated to leave a colourless liquid with a very potent aroma purified as stated.

a. 2-(*RS*)-*tert*-Butyl-4-(*R*)-isobutyl-1,3-oxathiolane **16**

Reaction was carried out as above using (*R*)-2-mercapto-4-methylpentan-1-ol **6** (780 mg, 5.8 mmol), pivalaldehyde (0.5 g, 0.6 mL, 5.8 mmol) in dry ether (7 mL) and boron trifluoride diethyl etherate (0.8 g, 0.7 mL, 5.8 mmol) in dry ether (3 mL) for 1 h. Kugelrohr distillation afforded the title compound (950 mg, 81%) as a colourless liquid, bp (oven temp.) 45 °C at 0.35 Torr as a 66:34 mixture of two diastereomers (Found: C, 64.71; H, 11.03%. $C_{11}H_{22}OS$ requires C, 65.29; H, 10.96%). HRMS (EI) *m/z* calcd for $C_{11}H_{22}OS$: 202.1391, found: 202.1395 [M]. ν_{max}/cm^{-1} 2930, 1450. major diastereomer *cis*-**16** ^{1}H NMR (300 MHz): 4.88 (1 H, s, CHBu^t), 3.98 (1 H, half AB pattern of d, *J* 10, 2, CH_2O), 3.78 (1 H, half AB pattern of d, *J* 10, 6, CH_2O), 3.45 (1 H, m, CHS), 1.63 (1 H, m, C*H*Me$_2$), 1.44 (2 H, m, CHC*H*$_2$CH), 0.97 (9 H, s, C*Me*$_3$), 0.89 (6 H, d, *J* 7, CH*Me*$_2$); ^{13}C NMR (75 MHz): 96.8 (CHO), 76.8 (CH_2O), 46.8 (CHS), 45.4 (CH_2), 34.7 (*C*Me$_3$), 26.7 (CH), 26.0 (C*Me*$_3$), 23.0 (Me), 21.8 (Me); minor diastereomer *trans*-**16** ^{1}H NMR (300 MHz): 4.95 (1 H, s, CHBu^t), 4.31 (1 H, d of d, *J* 9.3, 6, CH_2O), 3.44 (1 H, m, CHS), 3.35 (1 H, d of d, *J* 9.3, 9, CH_2O), 1.63 (1 H, m, C*H*Me$_2$), 1.44 (2 H, m, CHC*H*$_2$CH), 0.95 (9 H, s, C*Me*$_3$), 0.86 (6 H, d, *J* 7, CH*Me*$_2$). ^{13}C NMR (75 MHz): 96.5 (CHO), 77.5 (CH_2O), 47.7 (CHS), 42.5 (CH_2), 35.2 (*C*Me$_3$), 28.2 (CH), 25.8 (C*Me*$_3$), 23.0 (Me), 22.1 (Me). *m/z* (EI) 222 (M^+, 35%), 116 (44), 105 (25), 82 (46), 75 (100).

b. 4-(*R*)-Isobutyl-2-(*RS*)-phenyl-1,3-oxathiolane **17**

Reaction was carried out as above using (*R*)-2-mercapto-4-methylpentan-1-ol **6** (1.9 g, 14 mmol), benzaldehyde (1.5 g, 1.4 mL, 14 mmol) in dry THF (35 mL) and boron trifluoride diethyl etherate (2.0 g, 1.7 mL, 14 mmol). This solution was heated for 1 h. Kugelrohr distillation afforded the title compound (3.2 g, $>$ 99%) as a colourless liquid, bp (oven temp.) 140 °C at 0.3 Torr as a 52:48 diastereomeric mixture. (Found: C, 69.44; H, 8.18%. $C_{13}H_{18}OS$ requires C, 70.23; H, 8.16%). HRMS (EI) *m/z* calcd for $C_{13}H_{18}OS$: 222.1078, found: 222.1086 [M]. ν_{max}/cm^{-1} 2930, 1450. major diastereomer *cis*-**17** ^{1}H NMR (300 MHz): 7.60–7.50 (2 H, m, Ph), 7.45–7.30 (3 H, m, Ph), 6.18 (1 H, s, PhCH), 4.15 (1 H, half AB pattern of d, *J* 7, 3, CH_2O), 4.03 (1 H, half AB pattern of d, *J* 7, 4, CH_2O), 3.91 (1 H, m, CHS), 1.70 (2 H, m, CHC*H*$_2$CH), 1.62 (1 H, m, C*H*Me$_2$), 1.00 (6 H, d, *J* 7, CH*Me*$_2$). ^{13}C NMR (75 MHz): 139.9 (Ph-C1), 128.8 (Ph, 2CH), 128.6 (Ph, 2CH), 126.8 (Ph-C4), 87.7 (CHO), 77.5 (CH_2O), 49.4 (CHS), 43.3 (CH_2), 28.2 (CH), 23.1 (Me), 22.2 (Me); minor diastereomer *trans*-**17** ^{1}H NMR (300 MHz): 7.60–7.50 (2 H, m, Ph), 7.45–7.30 (3 H, m, Ph), 6.12 (1 H, s, PhCH), 4.51 (1 H, d of d, *J* 7, 5, CH_2O), 3.76 (1 H, m, CHS), 3.61 (1 H, t, *J* 7, CH_2O), 1.70 (2 H, m, CHCH_2CH), 1.62 (1 H, m, C*H*Me$_2$), 1.00 (6 H, d, *J* 7, CH*Me*$_2$). ^{13}C NMR (75 MHz): 139.6 (Ph-C1), 128.6 (Ph, 2CH), 127.0 (Ph, 2CH), 126.8 (Ph-C4), 87.2 (CHO), 76.8 (CH_2O), 49.7 (CHS), 45.7 (CH_2), 27.2 (CH), 23.2 (Me), 22.0 (Me). *m/z* (EI) 202 (M^+, 10%), 145 (100), 83 (25).

c. Preparation of 2-(*R*)- and 2-(*S*)-benzoyl-4-(*R*)-isobutyl-1,3-oxathiolane **18**

A solution of (*R*)-2-mercapto-4-methylpentan-1-ol **6** (200 mg, 1.5 mmol), phenylglyoxal monohydrate (227 mg, 1.5 mmol) and a catalytic quantity of *p*-toluenesulfonic acid monohydrate (5 mg) in dry toluene (50 mL) was heated under reflux for 9 h. After cooling the toluene was evaporated and the residue added to ether (20 mL). This was washed

with saturated aqueous sodium hydrogen carbonate (2 × 25 mL), dried and evaporated. Purification by chromatography eluting with light petroleum/ether (4: 1) afforded two diastereomers of the title compound:

The 2,4-*cis* diastereomer **18a** (120 mg, 32%), Rf 0.48. HRMS (EI) *m/z* calcd for $C_{14}H_{19}O_2S$: 251.1106, found: 251.1112 [M + H]. ν_{max}/cm^{-1} 1705. ^1H NMR (300 MHz): 7.38 (5 H, m, Ph), 5.20 (1 H, s, PhCH), 4.04 (1 H, half AB pattern of d, *J* 12, 3, CH_2O), 3.94 (1 H, m, CHS), 3.66 (1 H, half AB pattern of d, *J* 12, 5, CH_2O), 1.80 (1 H, m, C*H*Me_2), 1.52 (2 H, t, J 7, CHC*H*$_2$CH), 0.98 (6 H, d, J 7, CH*Me*). ^{13}C NMR (75 MHz): 198.6 (C=O), 136.1 (Ph-C1), 128.7 (Ph-C4), 128.7 (Ph, 2CH), 128.0 (Ph, 2CH), 89.0 (CHO), 65.9 (CH_2O), 43.5 (CHS), 43.4 (CH_2), 22.9 (CH), 22.8 (Me), 21.9 (Me). *m/z* (EI) 251 ($M + H^+$, 80%), 222 (95), 116 (75), 105 (95), 75 (100).

The 2,4-*trans* diastereomer **18b** (43 mg, 11%), Rf 0.50. HRMS (EI) *m/z* calcd for $C_{14}H_{19}O_2S$: 251.1106, found: 251.1111 [M + H]. ν_{max}/cm^{-1} 1705. ^1H NMR (300 MHz): 7.40–7.35 (5 H, m, Ph), 5.08 (1 H, s, PhCH), 4.34 (1 H, d of d, *J* 12, 4, CH_2O), 4.00 (1 H, m, CHS), 3.66 (1 H, d of d, *J* 12, 10, CH_2O), 1.72 (1 H, m, C*H*Me_2), 1.52 (2 H, t, *J* 7, CHC*H*$_2$CH), 0.98 (6 H, d, *J* 7, CH*Me*$_2$). ^{13}C NMR (75 MHz): 199.0 (C=O), 136.3 (Ph-C1), 128.9 (Ph-C4), 128.7 (Ph, 2CH), 127.9 (Ph, 2CH), 86.9 (CHO), 70.3 (CH_2O), 43.7 (CHS), 41.7 (CH_2), 25.0 (CH), 22.9, 21.9 (Me). *m/z* (EI) 251 ($M + H^+$, 7%), 222, 116 (80), 105 (65), 75 (100); (CI) 251 ($M + H^+$, 100%), 235 (10), 221 (45), 209 (20), 159 (6).

11. Oxidation of chiral 1,3-oxathiolanes

a. 2-(*RS*)-*tert*-Butyl-4-(*R*)-isobutyl-1,3-oxathiolane *S*-oxide **19**

A solution of 2-(*RS*)-*tert*-butyl-4-(*R*)-isobutyl-1,3-oxathiolane **16** (360 mg, 1.8 mmol) in dry ether (5 mL) was added dropwise to a solution of *m*-CPBA (70–75%, 440 mg, 3.6 mmol) in dry ether (10 mL) stirred at 0 °C. After 3 h this was allowed to warm up to RT and stirred for a further 60 h. The mixture was then washed with saturated aqueous sodium bicarbonate (4 × 100 mL), dried and evaporated. Kugelrohr distillation of the residue afforded the title compound (370 mg, 85%) as a colourless liquid, bp (oven temp.) 120 °C at 0.5 Torr (Found: C, 59.85; H, 10.19. $C_{11}H_{22}O_2S$ requires C, 60.51; H, 10.16%) as a 34:66 mixture of two diastereomers. This compound showed a peculiar behavior upon distillation and gave a complete reversal of the diastereomeric ratio:- 2nd distillation bp (oven temp.) 120 °C at 0.5 Torr gave a 55: 45 mixture of two diastereomers; 3rd distillation bp (oven temp.) 120 °C at 0.5 Torr gave a 61: 39 mixture of two diastereomers; ν_{max}/cm^{-1} 2950, 1430. major diastereomer *cis*-**19a** (after 3rd distillation) ^1H NMR (300 MHz): 4.33 (1 H, half AB pattern of d, *J* 10, 4, CH_2O), 4.23 (1 H, half AB pattern, *J* 10, CH_2O), 4.03 (1 H, s, CHBu^t), 3.12 (1 H, t of d, *J* 8, 4, CHSO), 1.78 (2 H, m, CHC*H*$_2$CH), 1.35 (1 H, m, C*H*Me_2), 1.11 (9 H, s, C*Me*$_3$), 0.99 (6 H, d, *J* 7, CH*Me*$_2$). ^{13}C NMR (75 MHz): 121.5 (CHO), 73.2 (CH_2O), 65.5 (CHSO), 36.6 (CH_2), 33.2 (*C*Me_3), 26.9 (CH), 26.6 (C*Me*$_3$), 22.6, 22.3 (Me); minor diastereomer *trans*-**19b** ^1H NMR (300 MHz): 4.41 (1 H, d of d, *J* 10, 6, CH_2O), 4.03 (1 H, s, CHBu^t), 3.84 (1 H, t, *J* 10, CH_2O), 2.52 (1 H, m, CHSO), 1.78 (2 H, m, CHC*H*$_2$CH), 1.35 (1 H, m, C*H*Me_2), 1.09 (9 H, s, C*Me*$_3$), 0.94 (6 H, d, *J* 7, CH*Me*$_2$). ^{13}C NMR (75 MHz): 121.2 (CHO), 73.2 (CH_2O), 60.3 (CHSO), 33.8 (*C*Me_3), 30.4 (CH_2), 30.0 (CH), 26.3 (C*Me*$_3$), 22.6, 22.4 (Me).

b. 4-(*R*)-Isobutyl-2-(*RS*)-phenyl-1,3-oxathiolane *S,S*-dioxide **20**

A solution of 4-(*R*)-isobutyl-2-(*RS*)-phenyl-1,3-oxathiolane **17** (1.6 g, 7 mmol) in dry ether (20 mL) was added dropwise to a solution of *m*-CPBA (70–75%, 3.5 g, 14 mmol)

in dry ether (30 mL) at 0 °C. This was allowed to warm up to RT and after 40 h work up as above afforded the title compound as a 87:13 mixture of two diastereomers (4.6 g, 85%) as colourless needles, mp 119.5–120.5 °C. Recrystallisation from ethyl acetate–ether gave needles, mp 121–122 °C, of the pure major diastereomer *trans*-**20** suitable for X-Ray determination (Found: C, 61.25; H, 7.02% $C_{13}H_{18}O_3S$ requires C, 61.39; H, 7.13%). HRMS (EI) *m/z* calcd for $C_{13}H_{19}O_3S$: 255.1055, found: 255.1062 [M + H]. ν_{max}/cm^{-1} 1455, 1305; major diastereomer *trans*-**20** ^{1}H NMR (300 MHz): 7.42 (5 H, m, Ph), 5.10 (1 H, s, PhCH), 4.71 (1 H, d of d, *J* 11, 8, CH_2O), 3.84 (1 H, t, *J* 11, CH_2O), 3.35 (1 H, m, CHS), 1.95–1.75 (2 H, m, CHCH_2CH), 1.47 (1 H, m, C*H*Me$_2$), 1.00 (6 H, d, *J* 7, CH*Me*$_2$). ^{13}C NMR (75 MHz): 130.4 (Ph-C4), 129.5 (Ph-C1), 128.9 (Ph, 2CH), 127.6 (Ph, 2CH), 94.2 (CHO), 70.8 (CH_2O), 56.3 (CHS), 34.8 (CH_2), 26.2 (CH), 22.6, 22.4 (Me); minor diastereomer *cis*-**20** ^{1}H NMR (300 MHz): 7.42 (5 H, m, Ph), 5.24 (1 H, s, PhCH), 4.49 (1 H, half AB pattern of d, *J* 9, 6, CH_2O), 4.32 (1 H, half AB pattern of d, *J* 9, 3, CH_2O), 3.35 (1 H, m, CHS), 1.95–1.75 (2 H, m, CHCH_2CH), 1.47 (1 H, m, C*H*Me$_2$), 1.00 (6 H, d, *J* 7, CH*Me*$_2$). ^{13}C NMR (75 MHz): 130.4 (Ph-C4), 129.5 (Ph-C1), 128.9 (Ph, 2CH), 127.5 (Ph, 2CH), 93.9 (CHO), 70.4 (CH_2O), 55.8 (CHS), 36.7 (CH_2), 26.2 (CH), 22.7, 22.1 (Me). *m/z* (CI) 255 ($M + H^+$, 100%), 107 (9), 83 (4).

12. Pyrolysis of 4-(*R*)-isobutyl-2-(*RS*)-phenyl-1,3-oxathiolane *S,S*-dioxide **20**

FVP of the title compound (53 mg, 700 °C, 8.0×10^{-3} Torr) gave a liquid in the cold trap which consisted of benzaldehyde (60%) and 4-methylpent-1-ene (78%) by ^{1}H and ^{13}C NMR and GCMS. PhCHO ^{1}H NMR (300 MHz): 10.03 (1 H, s), 7.92–7.85 (2 H, m), 7.68–7.50 (3 H, m); ^{13}C NMR (75 MHz): 192.9 (CO), 136.9 (C), 135.0 (CH), 130.2, 129.5 (2CH); i-BuCH=CH_2 ^{1}H NMR (300 MHz): 5.88–5.68 (1 H, m), 5.06–4.95 (2 H, m), 1.93 (2 H, t, *J* 7), 1.62 (1 H, septet, *J* 7), 0.88 (6 H, d, *J* 7); ^{13}C NMR (75 MHz): 138.4 (CH), 115.8, 43.8 (CH_2), 28.5 (CH), 22.7 ($2CH_3$).

13. X-Ray structure determination

A colourless tablet ($0.40 \times 0.30 \times 0.15$ mm) of *trans*-**20** suitable for X-ray diffraction was obtained by recrystallisation from diethyl ether–ethyl acetate. The following data were obtained: $C_{13}H_{18}SO_3$, M = 254.34. Triclinic space group P1 (No. 1), $a = 5.952(2)$, $b = 10.920(3)$, $c = 5.580(2)$ Å, $\alpha = 100.49(3)$, $\beta = 108.52(3)$, $\gamma = 93.05(3)°$, $V = 335.7(2)$ Å^3, $Z = 1$, $D_c = 1.258$ g/mL, $R = 0.029$, $Rw = 0.023$ for 1247 observed reflections with $I > 3\sigma(I)$ and 152 parameters. Data were recorded at 293 K using MoK_α radiation and the structure was solved by direct methods and refined using full-matrix least squares analysis.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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