Structure and Absolute Stereochemistry of Thioacetal Sulphoxides Obtained by Fungal Metabolism of 2-Alkyl-1,3-Dithianes

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Monosulphoxide metabolites of 2-methyl-, 2-t-butyl-, 2,2-dimethyl-, and 2-methyl-2-t-butyl-1,3-dithiane have been isolated after addition of the thioacetals to growing cultures of the fungi *Aspergillus foetidus*, *Mortierella isabellina* and a *Helminthosporium* species. The optical yields of the chiral monosulphoxide metabolites (0—72%) were determined by n.m.r. analysis in (−)-phenyl- or 1-(+)-9-anthryl-2,2,2-trifluoroethanol–$CDCl_3$ solvent mixtures. The signs of Cotton effects obtained from c.d. spectra have been used to assign the absolute stereochemistry of the chiral thioacetal sulphoxides. Optically pure samples of 2,2-dimethyl-1,3-dithiane 1-oxide, *cis*-2-methyl-1,3-dithiane 1-oxide, and *trans*-2-methyl-1,3-dithiane 1-oxide, have been obtained by a chemical resolution method which provides confirmation of optical yields and absolute stereochemistry.

The fungal metabolism results indicate that the mono-oxygenase enzymes can stereodifferentiate between prochiral (diastereotopic) lone pairs on a sulphur atom and also between prochiral (enantiotopic) thioalkyl substituents on a carbon atom during the formation of monosulphoxides.

Thioacetal, thioacetal sulphoxide, and thioacetal sulphone groups have all been found in natural products. Thus, examples of both acyclic [*e.g.*, bismethylthiomethane, (**1**),[1] djenkolic acid, (**2**),[2] and *N*-acetyldjenkolic acid, (**3**)[3]] and cyclic [*e.g.*, trithiolanicin, (**4**)[4] and lanthionine, (**5**)[5]] thioacetals have been isolated from plants and micro-organisms.

$R^1CH_2SCH_2SCH_2R^2$ $\overline{SCH(Ph)SSCHPh}$ $\overline{CH_2SSCH_2SSS}$

(**1**) $R^1 = R^2 = H$ (**4**) (**5**)
(**2**) $R^1 = R^2 = CH(NH_2)CO_2H$
(**3**) $R^1 = CH(NH_2)CO_2H, R^2 = CH(NHAc)CO_2H$

$R^1CH_2SOCH_2SCH_2R^2$ $R^1CH_2SOCH_2SOCH_2R^2$

(**6**) $R^1 = R^2 = CH(NH_2)CO_2H$ (**10**) $R^1 = R^2 = CH(NH_2)CO_2H$
(**7**) $R^1 = CH(NH_2)CO_2H, R^2 = CH(NHAc)CO_2H$
(**8**) $R^1 = CH(CO_2H)NHCOCH_2CH_2CH(NH_2)CO_2H, R^2 = H$
(**9**) $R^1 = CH(CH_2OH)NHCOCH = CH$(4-methyluracil-5-yl), $R^2 = H$

$R^1CH_2SO_2CH_2SCH_2R^1$

(**11**) $R^1 = R^2 = CH(NH_2)CO_2H$

$RCH_2SOCH_2SO_2CH_2SOCH_2SOR$

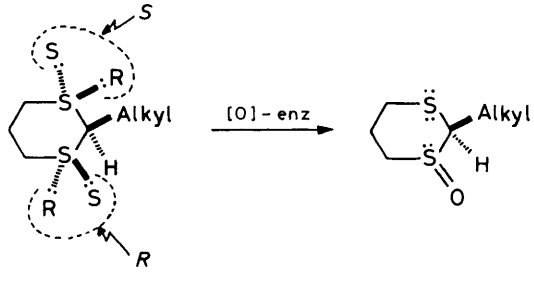
(**12**) $R = CH_2CH(CO_2H)NHCOCH_2CH_2CH(NH_2)CO_2H$

Similarly, djenkolic acid monosulphoxide (**6**),[6] *N*-acetyldjenkolic acid monosulphoxide (**7**),[6] γ-glutamylmarasmine (**8**),[7] and sparsomycin (**9**)[8,9] are examples of naturally occurring thioacetal monosulphoxides. More highly oxygenated thioacetal derivatives found in nature include the disulphoxide of djenkolic acid (**10**),[6] the monosulphone dichrostachinic acid (**11**),[10] and the sulphoxide sulphone lentinic acid (**12**).[11]

The mono-oxygenase-catalysed oxidation of sulphides to sulphoxides and sulphones is a common metabolic process and can account for the formation of thioacetal sulphoxides and sulphones. Thus, oxidation of the acyclic thioacetals 1,1-bismethylthio-3-phthalimidopropane (**13**)[12] and bis-*p*-tolylthiomethane (**14**)[13] and cyclic thioacetals 1,3-dithiane (**15**)[13] and 1,3,5-trithiane (**16**)[13] to the corresponding monosulphoxides by fungal enzymes has recently been reported.

Oxidation of the 1,3-dithiane ring system was not found to occur when ketones (**17**)[14] and (**18**)[15] were added to growing cultures of *Saccharomyces cerevisiae*. Enzyme-catalysed reduction to the corresponding alcohols, however, was observed,[14,15] indicating that the 1,3-dithiane ring can act as a carbonyl-protecting group for both chemical and enzymatic transformations.

A major objective of the present (and the preliminary)[16] study was to examine the ability of fungal mono-oxygenase-catalysed oxidation to occur with stereodifferentiation between prochiral lone pairs on a sulphur atom and between prochiral thioalkyl groups on a carbon atom using 2-alkyl 1,3-dithianes as substrates.



Previous studies have shown that the mono-oxygenase enzymes present in fungi could discriminate between the

$R^1CH(SR^2)_2$ $\overline{CH_2XCH_2SCH_2S}$ $\overline{CH_2[CH_2]_2SCH(R)S}$

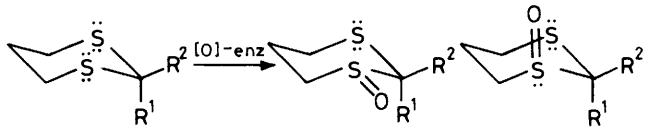
(**13**) $R^1 = \overline{COC_6H_4CONCH_2CH_2}$, $R^2 = Me$ (**15**) X = CH_2 (**17**) R = CH_2Ac

(**14**) $R^1 = H, R^2 = p$-tolyl (**16**) X = S (**18**) $R = CO(CH_2)_3CO_2R'$

prochiral lone pairs associated with a sulphur atom in acyclic sulphides[17,18] (enantiotopic lone pairs), in cyclic sulphides[19] (diastereotopic lone pairs), and in cyclic thioacetals[13] (enantiotopic lone pairs) during sulphoxide synthesis.

In order to establish the acceptability of 2-alkyl substituted cyclic thioacetals as substrates for sulphoxide formation by fungi, 2,2-dimethyl-1,3-dithiane (**19**) was added separately to growing cultures of *Aspergillus foetidus* (A), *Mortierella isabellina* (M), and a *Helminthosporium* species (H). The monosulphoxide metabolite (**20**) was isolated by continuous dichloromethane extraction of the culture medium and mycelium followed by column chromatographic (and in selected examples by preparative h.p.l.c.) purification on silica gel. The enantiomeric excess (e.e.) of sulphoxide (**20**) resulting from microbial transformation of thioacetal (**19**) was determined by n.m.r. analysis using (—)-(*R*)-2,2,2-trifluorophenylethanol as a co-solvent with $CDCl_3$. A stereo preference for the (−) enantiomer of (**20**) over the range 10—36% e.e. was observed for all fungi (Table 1).

Since virtually no preferential removal of the (+) enantiomer of (**20**) was detected using racemic 2,2-dimethyl 1,3-dithiane 1-oxide (**20**) as substrate, the optical activity observed resulted from asymmetric oxidation of thioacetal (**19**). The maximum enantiomeric excess observed (*ca.* 36%) was higher than that previously obtained by fungal oxidation of thioacetal (**15**) to 1,3-dithiane 1-oxide (22% e.e.) using similar fungi and conditions.[13]



$R^1 = R^2 = Me$ (**19**) (**20**)

$R^1 = H, R^2 = Me$ (**21**) (**22**) (**23**)

$R^1 = H, R^2 = Bu^t$ (**24**) (**25**) (**26**)

$R^1 = Me, R^2 = Bu^t$ (**27**) (**28**) (**29**)

Both 1,3-dithiane (**15**) and 2,2-dimethyl-1,3-dithiane (**19**) are conformationally mobile molecules at ambient temperature which appear to exist preferentially in the chair conformation (by n.m.r. analysis). A similar mobility was associated with sulphoxide (**20**) which preferred a chair (or twist) conformation with the oxygen atom equatorial (≥80% equatorial).[20]

Fungal metabolism of the 2-alkyl substituted thioacetals (**21**) and (**24**) and the thioacetal (**27**) under similar conditions yielded the corresponding sulphoxides (**22**), (**23**), **25**), (**26**), and (**28**) of optical yields indicated in Table 2. Of the three fungi examined, *A. foetidus* and the *Helminthosporium* species gave comparable yields of monosulphoxides which were generally higher than those obtained from *M. isabellina*. The relative proportions of *cis*- and *trans*-isomers obtained from thioacetals (**21**), (**24**) and (**27**) were very similar for each micro-organism and were comparable with the ratio obtained by chemical oxidation. Thus thioacetals (**21**) and (**24**) gave essentially the same yields of *cis* (**23**) (8%) and (**26**) (10%) and *trans* (**22**) (92%) and (**25**) (90%) sulphoxides after oxidation with $NaIO_4$.[20,21] Oxidation of 2-methyl-2-t-butyl-1,3-dithiane (**27**) under similar conditions gave the *trans*-sulphoxide isomer (**28**) exclusively, *i.e. cis*-isomer (**29**) was not detected under any oxidation conditions. Since a t-butyl substitutent was present in the sulphoxides (**25**)—(**28**)

Table 1. Fungal metabolism of 2,2-dimethyl-1,3-dithiane (**19**) and 2,2-dimethyl-1,3-dithiane 1-oxide (**20**)

Fungus[a]	Sulphoxide (% yield,[b] $[\alpha]_D$,[c] % e.e.[d])
A	(**20**)[e] (34, (−) 20.3°, 24[f]), (36, (−),[g] 18[f])
A	(**20**)[f] (43, (+),[g] 4[f])
H	(**20**)[e] (30, (−) 33.8°, 36[f]), (27, (−),[g] 16[f])
H	(**20**)[f] (43, (±),[g] 0[f])
M	(**20**)[d] (20, (−) 22.5°, 21[f]) (16, (−),[g] 10[f])
M	(**20**)[f] (40, (±) 0, 0[f])

[a] A ≡ *Aspergillus foetidus*, H ≡ *Helminthosporium* species, M ≡ *Mortierella isabellina*. [b] Yields obtained after purification by silica-gel chromatography.[c] Measured in EtOH solution (*ca.* 0.01 g/ml) after further purification by preparative h.p.l.c. on silica-gel. Where purification involved column chromatography alone the sign of the $[\alpha]_D$ value is given. [d] N.m.r. (250 MHz) analysis in $CDCl_3$ (−)-phenyl-2,2,2-trifluoroethanol–$CDCl_3$ using the methyl singlet at δ 1.63. [e] Isolated after fungal oxidation of the parent thioacetal. [f] Recovered after addition of the racemic sulphoxide to the fungi. [g] Sign of $[\alpha]_D$ associated with the predominant enantiomer which was deduced by n.m.r. analysis.

Table 2. Fungal metabolism of 2-methyl-1,3-dithiane (**21**), 2-t-butyl-1,3-dithiane (**24**), and 2-t-butyl-2-methyl-1,3-dithiane (**27**) and the corresponding monosulphoxides

Fungus[a]	*trans*-Sulphoxide (% yield,[b] $[\alpha]_D$,[c] % e.e.)	*cis*-Sulphoxide (% yield,[b] $[\alpha]_D$,[c] % e.e.)
A	(**22**)[d] (27, (+) 1.6°, 8[e]), (28, (+) 1.6°, 8[e])	**23**[d] (2, (+) 4.8°, 2[f]) (2, (+) 6.6°, 3[f])
A	(**22**)[g] (30, (+) 3.5°, 10[e]), (29, (+),[h] 2[e])	**23**[i] (26, (±),[h] 3[f])
H	(**22**)[d] (28, (−), 17.1°, 27[e]), (28, (−) 22.8°, 36[e])	**23**[d] (2, (−) 71.5°, 33.5[f])
H	(**22**)[g] (31, (±),[h] 2[e]), (33, (±),[h] 1[e])	**23**[i] (28, (±),[h] 0[f])
M	(**22**)[d] (9, (−) 11.2°, 19[e]), (11, (−),[h] 12[e])	**23**[d] (1, (−) 39.0°, 21[f])
M	(**22**)[g] (38, (±),[h] 2[e]), (40, (±),[h] 2[e])	**23**[h] (35, (±),[h] 1[f])
A	(**25**)[d] (26, (−),[h] 2[f]), (30, (−),[h] 10[f])	**26**[d] (6, (+),[h] 20[f]), (5, (+),[h] 22[f])
A	(**25**)[j] (30, (−),[h] 14[f])	**26**[j] (3, (±),[h] 0[f])
H	(**25**)[d] (22, (−) 5.4°, 14[f]), (20, (−) 13.1°, 35[f])	**26**[d] (4, (+) 80.3°, 65[f]), (5, (+) 83.0°, 72[f])
H	(**25**)[j] (34, (±),[h] 0[f])	**26**[j] (3, (±),[h] 0[f])
M	(**25**)[d] (29, (+) 5.8°, 10[f]), (26, (±), 0[f])	**26**[d] (7, (±),[h] 0), (4, (±),[h] 0)
M	(**25**)[j] (24, (+),[h] 6[f])	**26**[j] (3, (±),[h] 0)
A	(**28**)[d] (30, (+) 6.4°, 8[f])	
A	(**28**)[g] (47, (±),[h] 0[f])	
H	(**28**)[d] (24, (±),[h] 0[f])	
H	(**28**)[g] (50, (±),[h] 0[f])	
M	(**28**)[d] (0, −, −)	
M	(**28**)[g] (0, −, −)	

[a–c] See corresponding footnotes in Table 1. [d] See footnote *e* in Table 1. [e] N.m.r. (250 MHz) analysis in $CDCl_3$–1-(+)-9-anthryl-2,2,2-trifluoroethanol using the methyl doublet at δ 1.65. [f] N.m.r. (250 MHz) analysis in $CDCl_3$–(−)-phenyl-2,2,2-trifluoroethanol using the methyl doublet at δ 1.64. [g] See footnote *f* in Table 1. [h] See footnote *g* in Table 1. [i] Sulphoxide added as a racemic isomeric mixture of (**22**):(**23**) (13:87). [j] Sulphoxide added as a racemic isomeric mixture of (**25**):(**26**) (8:92).

to act as a conformational anchor, equilibration between chair conformations having both axial and equatorial oxygen atoms did not occur. The latter type of interconversion occurs with conformationally mobile sulphoxides, *e.g.* (**22**) and (**23**), but with a preference toward the conformer with an equatorial oxygen atom.[20] Both chemical and enzyme-catalysed oxidations thus occur with a strong affinity being shown for the equatorial lone pair on each sulphur atom, *i.e.* preferential *trans*-sulphoxide formation.

The degree of asymmetric synthesis occurring during fungal enzyme-catalysed oxidation of the sulphides (**21**) and (**24**) appeared to be higher with the *Helminthosporium* species where a range of 33—72% e.e. was observed. Control experiments involving addition of the racemic sulphoxides (**22**), (**23**), (**25**), (**26**), and (**28**) to each of the fungi in turn showed that preferential removal of one enantiomer could account for the optical activity of the *trans*-sulphoxides (**22**) and (**25**) and the *cis*-sulphoxide (**23**) after addition of the corresponding thioacetals to cultures of *A. foetidus*.

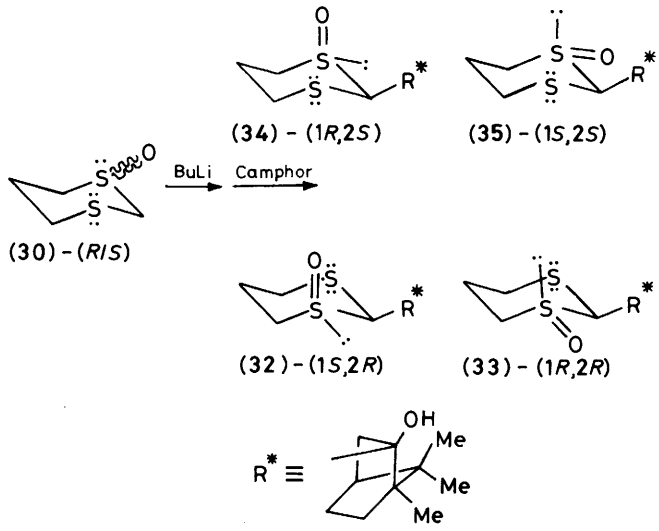
Although the relative (*cis–trans*) stereochemistry of sulphoxides (**22**), (**23**), (**25**), (**26**), and (**28**) had previously been determined on the basis of n.m.r. and t.l.c. characteristics,[20,21] they had not been obtained in optically active form and thus the absolute stereochemistry was unknown.

Individual enantiomers of 1,3-dithiane 1-oxide (**30**) have been obtained from the camphor adducts (**32**) and (**33**) after base catalysed cleavage.[22] Using this method in the present study a mixture of diastereoisomers (**32**—**34**) (Scheme 1) was obtained whose ratio (n.m.r. analysis) varied according to the work-up procedure. Preparative h.p.l.c. yielded three fractions, (a), (b) and (c).

Fraction (c) (k^1 = 5.65) contained one pure diastereoisomer which crystallized from solution {m.p. 206 °C, $[\alpha]_D$ +23° (EtOH), δ(2′-H) 3.87} and which gave (+)-(1*R*)-1,3-dithiane 1-oxide (**30**) upon treatment with KOH. The latter enantiomer could have been formed from either the (1*R*,2*R*)-(**33**) or (1*R*,2*S*)-(**34**) diastereoisomers.

Fraction (b) (k^1 = 4.40) also consisted of a single diastereoisomer {m.p. 190—191 °C, $[\alpha]_D$ −72.3° (EtOH), δ(2′-H) 3.78} which yielded (−)-(1*S*)-1,3-dithiane 1-oxide (**30**) by base-catalysed cleavage. Fraction (b) may thus be either (1*S*,2*R*)-(**32**) or (1*S*,2*S*)-(**35**).

Fractions (b) and (c) appeared to have very similar characteristics to those reported[22] for the (1*S*,2*R*)-(**32**) and (1*R*,2*R*)-(**33**) camphor adducts, respectively. Since, however, the first h.p.l.c. fraction (a) (k^1 = 3.50) appeared to contain the remaining two diastereoisomers [δ(2′-H) 3.74 and 3.92] which could not be separated, the assignment of absolute stereochemistry at the chiral C-2 carbon atom in fractions (b) and (c) should be regarded as tentative.



Scheme 1.

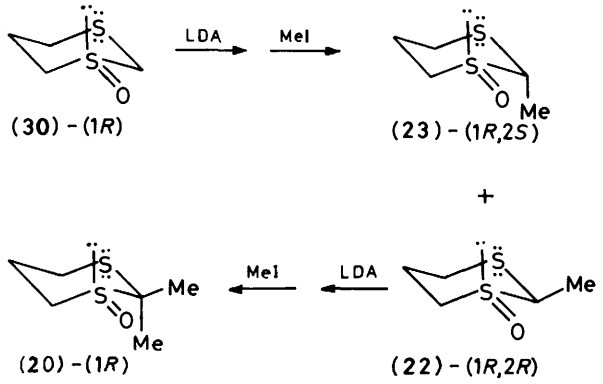
A stepwise methylation sequence of (+)-(1*R*)-1,3-dithiane 1-oxide (**30**) gave initially a mixture of (+)-(1*R*,2*R*)-*trans*-2-methyl-1,3-dithiane 1-oxide (**22**) and (+)-(1*R*,2*S*)-*cis*-2-methyl-1,3-dithiane 1-oxide (**23**) which were separated by preparative h.p.l.c. Methylation of the latter sulphoxide under identical conditions yielded (+)-(1*R*)-2,2-dimethyl-1,3-dithiane 1-oxide (**20**) (Scheme 2). By this stereochemical correlation sequence it has thus been possible to assign absolute stereochemistry to individual enantiomers of the 1,3-dithiane 1-oxides (**20**), (**22**), (**23**), and (**25**) using the unequivocally established configuration of sulphoxide (**30**)[22] as a reference. Attempts to attach a t-butyl group at the 2-position of 1,3-dithiane 1-oxide (**30**) using the usual alkylation route were unsuccessful presumably due to the larger steric requirements of the t-butyl group.

The inherently dissymmetric sulphoxide chromophore has previously been used in circular dichroism studies[23] and thus a

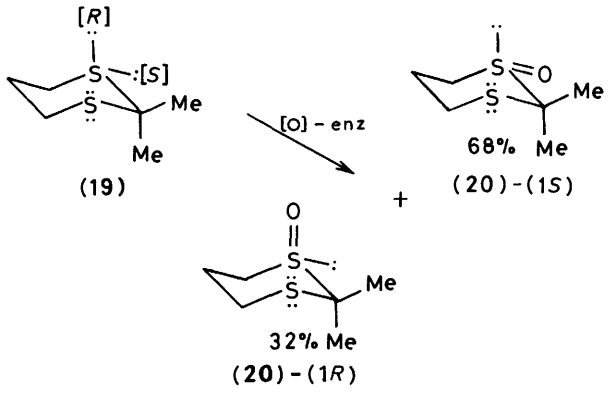
Table 3. Circular dichroism data and absolute stereochemistry of chiral 1,3-dithiane 1-oxides

Sulphoxide	% e.e.	λ(nm)[a]	Δξ[a]	λ(nm)[a]	Δξ[a]	$[\alpha]_D$ (EtOH)	Configuration
(**30**)	100[b]	234	+14.1	203	−10.1	(+)	(1*R*)
(**23**)	36[c]	232	−8.2	200	+3.3	(+)	(1*S*,2*R*)
(**23**)	100[b]	231	+21.0	203	−8.2	(−)	(1*R*,2*S*)
(**22**)	27[c]	235	−5.4	203	+8.0	(−)	(1*S*,2*S*)
(**22**)	100[b]	236	+18.7	203	−27.9	(+)	(1*R*,2*R*)
(**20**)	36[c]	232	−8.9	204	+7.5	(−)	(1*S*)
(**33**)	100[b]	237[d]	+14.8[d]	198[d]	−18.5[d]	(+)	(1*R*,2*R*)
(**32**)	100[b]	235[d]	−19.6[d]	198[d]	+20.5[d]	(−)	(1*S*,2*R*)
(**26**)	72[c]	245	−2.6	215	+25.2	(+)	(1*S*,2*R*)
(**25**)	35[c]	237	−8.2	204	+9.6	(−)	(1*S*,2*S*)
(**28**)	8[c]	235	+1.7	207	−1.2	(+)	(1*R*,2*R*)
(**30**)	100[b]	231[e]	+14.0[e]	201[e]	+4.4[e]	(+)	(1*R*)
(**23**)	100[b]	228[e]	+9.2[e]	199[e]	+26.0[e]	(−)	(1*R*,2*S*)
(**22**)	100[b]	233[e]	+14.8[e]	195[e]	−17.5[e]	(+)	(1*R*,2*R*)

[a] Solvent used was either cyclohexane or 3-methylpentane at concentrations of 2.5—3.0 mmol. [b] Obtained by chemical resolution method. [c] Obtained as a fungal metabolite. [d] In cyclohexane–priopionitrile (9:1). [e] In ethanol.



Scheme 2.



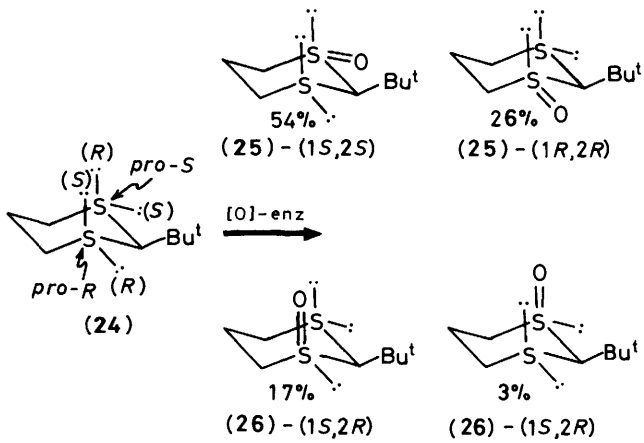
c.d. investigation of the chiral sulphoxides (**20**), (**22**), (**23**), (**25**), (**26**), (**28**), **30**), (**33**), and (**35**) was undertaken. Mislow *et al*[23] have proposed an empirical rule correlating the sign of Cotton effect centred at 205—210 nm with the absolute stereochemistry of the chiral methyl alkyl sulphoxide. Thus, a negative Cotton effect in this range was associated with an *R*-configuration.

Thioacetal sulphoxides contain both a sulphoxide and a sulphide chromophore. The latter chromophore may be classified as inherently symmetric in an asymmetric environment (the chiral sulphoxide group). Circular dichroism studies on chiral cyclic sulphides indicate that absorption can also occur in the range 209—215 nm and around 245 nm.[24,25] In general, the sulphoxide chromophore appears to be stronger and thus the Cotton effects of the chiral compounds shown in Table 3, which occur over the range 195—215 nm, have been mainly attributed to this chromophore. The Cotton effects found at 228—245 nm are clearly associated with the sulphide chromophore and in hydrocarbon solvents have an opposite sign to that shown by the sulphoxide group. It is noteworthy that in the c.d. spectra of sulphoxides (**30**), (**23**), (**22**), (**20**), (**32**), and (**33**) (whose absolute stereochemistry had been determined by stereochemical correlation methods) a negative Cotton effect centred around 198—204 nm was associated with a (1*R*)-configuration in accord with predictions based on the Mislow correlation.[23] This configuration was also found to be associated with the positive Cotton effect centred at 231—237 nm due to the sulphide chromophore. The latter method for configurational assignment appears to be valid only when the c.d. spectra are obtained in hydrocarbon solvents. In ethanol the sign of Cotton effect at *ca.* 230 nm was reversed for thioacetal sulphoxides (**22**), (**23**), and (**30**).

The bisignate c.d. pattern shown by thioacetal sulphoxides (**30**), (**23**), (**22**), (**20**), (**32**), and (**33**) (in hydrocarbon solvents) has also been observed for compounds (**26**), (**25**), and (**28**) and thus has been used to assign absolute stereochemistry to these examples (Table 3). The Mislow correlation has also been successfully applied to acyclic chiral thioacetal sulphoxides related to sparsomycin and now appears to be generally applicable to optically active monosulphoxides of thioacetals.[8]

The absolute stereochemistry of the thioacetal sulphoxide metabolites shown in Tables 1—3 can be used to determine the selectivity of fungal mono-oxygenase enzymes for particular sulphur atoms and for particular lone pairs in each sulphur atom of the 1,3-dithiane. This concept is exemplified by reference to the metabolism of thioacetals (**19**) and (**24**) by the *Helminthosporium* species. These examples have been selected since no evidence of preferential removal of either *cis*-or *trans*-isomer or of one enantiomer of the sulphoxide metabolites during the microbiological transformation was observed. A clear preference for the *pro-S* (68%) over the *pro-R* (32%) lone pair during oxidation of thioacetal (**19**) was obtained.

Product analysis suggests that oxidation of the thioacetal (**24**) in the *Helminthosporium* species occurs with an optimal preference (68%) for the *pro-S* group during equatorial attack, compared with the *pro-R* thioalkyl group (32%). Conversely, axial oxidation occurs with a marked selectivity for the *pro-R* (86%) rather than the *pro-S* (14%) thioalkyl group. Taking the relative yields of *cis*-(**26**) and *trans*-(**25**) sulphoxides, and the



optical yields of each into account, a resultant stereopreference for the *pro-S* thioalkyl group (57%) was observed. This result provides the first evidence that mono-oxygenase enzymes can stereodifferentiate between prochiral thioalkyl groups during sulphoxide formation.

Experimental

N.m.r. spectra were obtained using a Bruker Model WH250 instrument with $CDCl_3$ as solvent and tetramethylsilane as internal standard. The enantiomeric excess for each sulphoxide was determined by n.m.r. analysis with $CDCl_3$ as solvent containing either (−)-phenyl-2,2,2-trifluoroethanol (Burdick and Jackson Laboratories) or 1-(+)-9-anthryl-2,2,2-trifluoroethanol (Aldrich Chemical Co.). In a typical experiment the chiral sulphoxide (*ca.* 0.03 g) and chiral alcohol (*ca.* 0.06 g) were dissolved in $CDCl_3$ (1 ml).

Optical rotations were determined at 589 nm using a Perkin-Elmer Automatic Polarimeter, Model 241 with solutions at a concentration of *ca.* 0.01 g/ml in the specified solvent.

Analytical h.p.l.c. separations were obtained using a Spectra Physics Model 3500B instrument and a Partisil (4.6 × 250 mm) column with a flow rate of 2 ml/min. Preparative h.p.l.c. separations were achieved using a Pye-Unicam Model LC-

XPD or a Perkin-Elmer Model 3B instrument in conjunction with a Whatman Magnum 9 silica gel column (10 × 50 mm) at a flow rate of 4—5 ml min^{-1}.

Circular dichroism curves were obtained using a Jasco model J4OCS instrument with cyclohexane, 3-methylpentane, or ethanol as solvents at concentrations of *ca.* 0.2—0.5 mg/ml.

The fungal strains used and the conditions employed for the microbiological transformations were identical with those reported previously.[13] Preliminary purification of sulphoxides extracted from the culture medium and mycelium (continuous CH_2Cl_2 extraction, 7 days) was carried out by column chromatography using silica-gel (Crasfield Sorbsil M60). The thioacetals were eluted with light petroleum (b.p. 40—60 °C) while the monosulphoxides were eluted using diethyl ether–methanol.

Thioacetal (**15**) was commercially available (Aldrich Chem. Co.). Thioacetals (**19**), (**21**), (**24**), and (**27**) were synthesized by acid-catalysed condensation of the aldehyde or ketone with propane-1,3-dithiol according to the literature methods:[20,21,26] (**19**) 78% yield, b.p. 106 °C/25 mmHg (lit.,[20] 102 °C/24 mmHg). (**21**) 74% yield, b.p. 55 °C/2.5 mmHg (lit.,[26] 79—80 °C/10 mmHg). (**24**) 60% yield, b.p. 114 °C/17 mmHg (lit.,[20] 120 °C/22 mmHg). (**27**) 86% yield, b.p. 128 °C/17 mmHg, m.p. 30 °C (lit.,[20] 35 °C).

Spectral data for compounds (**19**), (**21**), (**24**), and (**27**) were identical with literature values.

Thioacetal monosulphoxides (**20**), (**22**), (**23**), (**25**), (**26**), and (**28**) were synthesized by the standard sodium metaperiodate oxidation procedure.[20] Product mixtures of sulphoxides (**22**)–(**23**) and (**25**)–(**26**) were separated by preparative h.p.l.c. using a Partisil column and 5% propan-2-ol in dichloromethane as eluant: (**20**) 64% yield, b.p. 110 °C/1.5 mmHg (lit.,[20] 98—100 °C/0.15 mm Hg): (**22**)–(**23**) 90% yield (96:4), α 1.27. (**22**) m.p. 95 °C (lit.,[21] 92—94 °C); (**23**) m.p. 59—60 °C (lit.,[21] 60—63 °C); (**25**)–(**26**) 71% yield (90:10), α 1.28; (**25**) m.p. 91—92 °C (lit.,[20] 91—92 °C); (**26**) m.p. 193—194 °C (lit.[20] 194—195 °C). (**28**) 95% yield, m.p. 77—78 °C (lit.[20] 81—83 °C).

Optically active sulphoxides (**20**), (**22**), (**23**), (**25**), (**26**), and (**28**) obtained by fungal oxidation were purified by column chromatography (silica gel eluting with diethyl ether–methanol), or by preparative h.p.l.c. Samples of both racemic and optically active sulphoxides were spectrally identical (n.m.r. and i.r.) and corresponded to the literature values. Optical rotations are recorded in Tables 1 and 2).

Optically pure samples of 1,3-dithiane 1-oxide (**15**) were obtained by the method of Bryan *et al.*[22] When the product mixture from treatment of racemic sulphoxide (**15**), butyllithium and camphor in THF solution was allowed to warm up from −70 °C to +15 °C before quenching with saturated ammonium chloride, a mixture of diastereoisomers was obtained (from n.m.r. analysis of the 2′-H signals); δ(2′-H) 3.74 (53%), 3.87 (6%), 3.92 (26%), and 3.78 (15%). When quenching occurred at −70 °C a different diastereoisomeric ratio was obtained; δ(2′-H) 3.74 (23%), 3.87 (50%), 3.92 (5%), and 3.78 (22%).

A partial separation of diastereoisomers was obtained by preparative h.p.l.c. separation (eluting with 5% propan-2-ol in dichloromethane) and three fractions were obtained: *Fraction* (*a*): k^1 = 3.50. Singlets at δ 3.74 and 3.94 for 2′-H were present indicating that a mixture of two diastereoisomers was present which was not separated. It was not possible to characterize the individual diastereoisomers in this mixture by the normal methods (m.p., $[\alpha]_D$).

Fraction (*b*): k^1 = 4.40, m.p. 190—191 °C, $[\alpha]_D$ −72.3° (EtOH), δ(2′-H) 3.78, *m/z* 288 (M^+, 2.2), 271 (10), 166 (91), and 151 (62). Treatment of fraction (b) with KOH gave (1*S*)-1,3-dithiane 1-oxide (**15**, $[\alpha]_D$ −224° (EtOH). Literature data for (1*S*,2*R*)-(**32**):[22] m.p. 194—195 °C, $[\alpha]_D$ −74.4° (EtOH), δ(2′-H) 3.74, *m/z* 288 (M^+, 17), 271 (35), 166 (100), 151 (45). KOH treatment gave (1*S*)-(**15**), $[\alpha]_D$ −224° (EtOH).

Fraction (*c*): k^1 = 5.65, m.p. 206 °C, $[\alpha]_D$ +23° ($CHCl_3$), δ(2′-H) 3.87, *m/z* 288 (M^+, 8), 271 (16), 166 (100). Treatment of fraction (c) with KOH gave (1*R*)-1,3-dithiane 1-oxide (**15**), $[\alpha]_D$ +227° (EtOH). Literature data for (1*R*,2*R*)-(**32**):[22] m.p. 216—218 °C, $[\alpha]_D$ +25.9 ($CHCl_3$), δ(2′-H) 3.82, *m/z* 288 (M^+, 14), 271 (16), 166 (100). KOH cleavage gave (1*R*)-1,3-dithiane 1-oxide (**15**), $[\alpha]_D$ +230° (EtOH).

(+)-(1R,2R)-trans-2-*Methyl*-1,3-*dithiane* 1-*Oxide* (**22**) *and* (+)-(1R,2S)-cis-2-*Methyl*-1,3-*dithiane* 1-*Oxide* (**23**), *and* (1R)-2,2-*Dimethyl*-1,3-*dithiane* 1-*Oxide* (**20**).—(+)-(1*R*)-1,3-Dithiane 1-oxide (**15**) was treated with lithium di-isopropylamide and methyl iodide according to the literature procedure.[21] The crude product mixture was found to consist of the *trans* (**22**) (70%) and *cis* (**23**) (30%) sulphoxides which were separated by preparative h.p.l.c. (+)-(1*R*,2*R*)-*trans*-2-Methyl-1,3-dithiane 1-oxide (**22**): yield 36%, m.p. 119—120 °C, $[\alpha]_D^{20}$ = +62.1° (EtOH) (Found: *M*, 150.017 40. Calc. for $C_5H_{10}S_2O$: *M*, 150.017 31). Spectral data were identical with the racemic sample.

(1*R*,2*S*)-*cis*-2-Methyl-1,3-dithiane 1-oxide (**23**): yield 25%, m.p. 71—72 °C, $[\alpha]_D^{20}$ = +201° (EtOH) (Found: *M*, 150.017 40. Calc. for $C_5H_{10}S_2O$: *M*, 150.017 31). Spectral data were identical with the racemic sample. Further methylation of (**22**) under identical conditions gave (1*R*)-2,2-Dimethyl-1,3-dithiane 1-oxide (**20**) which was purified by h.p.l.c. Yield 25%, oil, $[\alpha]_D^{20}$ = +99.3° (EtOH) (Found: *M*, *m/z* 164.033 01. Calc. for $C_6H_{12}S_2O$: *M*, 164.032 95). The optically pure sample of (+)-(**22**) was spectrally indistinguishable from a racemic sample.

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