# Dioxygenase-catalysed mono-, di- and tri-oxygenation of dialkyl sulfides and thioacetals: chemoenzymatic synthesis of enantiopure *cis*-diol sulfoxides

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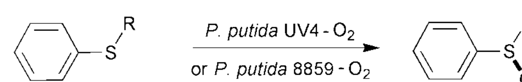
Toluene dioxygenase (TDO)-catalysed monooxygenation of methylsulfanylmethyl phenyl sulfide **1** and methylsulfanylmethyl 2-pyridyl sulfide **4**, using whole cells of *Pseudomonas putida* UV4, occurred exclusively at the alkyl aryl sulfur centre to yield the alkyl aryl sulfoxides **2** and **5** respectively. These sulfoxides, accompanied by the dialkyl sulfoxides **3** and **6**, were also obtained from naphthalene dioxygenase (NDO)-catalysed sulfoxidation of thioacetals **1** and **4** using intact cells of *P. putida* NCIMB 8859. Enzymatic oxidation of methyl benzyl sulfide **7**, 2-phenyl-1,3-dithiane **19**, and 2-phenyl-1,3-dithiolane **23**, using TDO, gave the corresponding dialkyl sulfoxides **8**, **20** and **24** as minor bioproducts. TDO-catalysed dioxygenation of the alkyl benzyl sulfides **7**, **15** and **17** and the thioacetals **19** and **23**, with *P. putida* UV4, yielded the corresponding enantiopure *cis*-dihydrodiols **9**, **16**, **18**, **21** and **25** as major metabolites and *cis*-dihydrodiol sulfoxides **14**, **22** and **26** as minor metabolites, resulting from a tandem trioxygenation of substrates **7**, **19** and **23** respectively. Chemical oxidation, of the enantiopure *cis*-dihydrodiol sulfides **9**, **16**, **18** and **21** with dimethyldioxirane (DMD), gave separable mixtures of the corresponding pairs of *cis*-dihydrodiol sulfoxide diastereoisomers **14** and **27**, **28** and **29**, **30** and **31**, **22** and **32**. While dialkyl sulfoxide bioproducts **3**, **6**, **20** and **24** were of variable enantiopurity (27–≥98% ee), alkyl aryl monosulfoxides **2** and **5**, *cis*-dihydrodiols **9**, **16**, **18**, **21** and **25** and *cis*-dihydrodiol sulfoxide bioproducts **14**, **22** and **26** were all single enantiomers (≥98% ee). The absolute configurations of the products, obtained from enzyme-catalysed (TDO and NDO) and chemical (DMD) oxidation methods, were determined by stereochemical correlation, circular dichroism, and X-ray crystallographic methods.

## Introduction

Dioxygenase enzymes, present in the soil bacterium *Pseudomonas putida* have been found to catalyse different types of oxidation on a remarkably wide range of substrates, generally with a high degree of regio- and stereo-selectivity.[1–3] In addition to the well-documented reports of dioxygenase-catalysed *cis*-dihydroxylation of arene and alkene substrates, the enzymes have also been found to catalyse monohydroxylations at activated carbon (benzylic or allylic)[4–9] or sulfur atoms (alkyl aryl sulfides)[10–13] and desaturation (dehydrogenation at aryl substituted carbon–carbon single bonds).[14–16] During the course of our studies on dioxygenase-catalysed reactions we have reported tandem biotransformations involving bis-benzylic hydroxylations of 2-substituted indanes[8] (non-vicinal diol formation), benzylic hydroxylation–*cis*-dihydroxylation[9] (trihydroxylation), bis-*cis*-dihydroxylations of tricyclic and tetracyclic arenes[17,18] (tetrahydroxylation), and desaturation–*cis*-dihydroxylation of dihydroarenes.[16] A new type of dioxygenase-catalysed trioxygenation, *i.e.* an arene *cis*-dihydroxylation–sulfoxidation biotransformation sequence, is presented in this study.

Dioxygenase enzymes in *P. putida* UV4, a source of TDO, and *P. putida* NCIMB 8859, a source of NDO, have earlier been used to obtain a series of sulfoxides from monooxygenation of the corresponding alkyl aryl sulfides (Scheme 1).[12] Sulfoxidation, using *P. putida* UV4, was found to be the strongly preferred metabolic pathway for alkyl phenyl sulfides rather than arene *cis*-dihydroxylation. Conversely, arene *cis*-dihydroxylation was found to occur much more readily when the dialkyl sulfide, benzyl methyl sulfide **7**, was used as substrate with *P. putida* UV4.[9] A preliminary investigation[11] of the TDO-catalysed oxidation of 2-phenyl-1,3-dithiane **19** indicated that the enantiopure *cis*-dihydrodiol **21** and monosulfoxide **20** were the major bioproducts. Formation of a single enantiomer of sulfoxide **20** was consistent with stereoselective oxygenation at one of the two prochiral (enantiotopic) sulfur atoms and one of the two (diastereotopic) prochiral lone pairs. A comparative study of the dioxygenase-catalysed sulfoxidation of alkyl aryl and dialkyl sulfides, and an evaluation of the potential of *cis*-dihydrodiol moiety of an enantiopure bioproduct in chirality transfer to an exocyclic sulfur atom by chemical oxidation to yield single enantiomer dialkyl sulfoxides, were objectives of this study.




**Scheme 1**

## Results and discussion

To date more than thirty examples of alkyl aryl sulfoxides with a high enantiomeric excess (≥90% ee) have been produced by

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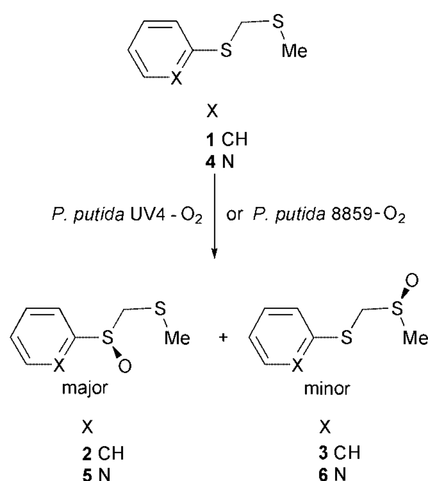
TDO- or NDO-catalysed sulfoxidation of alkyl aryl sulfides.[10–13] The alkyl aryl sulfoxides, formed *via* dioxygenase-catalysed monooxygenation of the sulfide precursors, were not contaminated by sulfones[10–13] from further oxidation (dioxygenation). This was an advantage over many other microbial oxygenation methods.[19–23] Earlier biotransformation studies of thioacetals using fungi[24–28] yielded mono- and bis-sulfoxides of relatively low ee values (0–70%), but recently employment of intact fungal and bacterial systems[21,29] have given sulfoxides with improved ee values (9–98%) from several thioacetal substrates containing dialkyl sulfur centers. However, in the latter studies the microbial species were known to contain monooxygenase enzymes and generally both sulfoxide and sulfone bioproducts were isolated.

### (a) Dioxygenase-catalysed monooxygenations: sulfoxidation at dialkyl sulfur centres

As an extension of our studies of dioxygenase-catalysed asymmetric oxidation of alkyl aryl sulfides,[11,12] the thioacetals methylsulfanylmethyl phenyl sulfide **1** and methylsulfanylmethyl 2-pyridyl sulfide **4** were selected as potential substrates for the TDO and NDO enzymes present in *P. putida* UV4 and 8859 respectively (Scheme 2).




**Scheme 2**

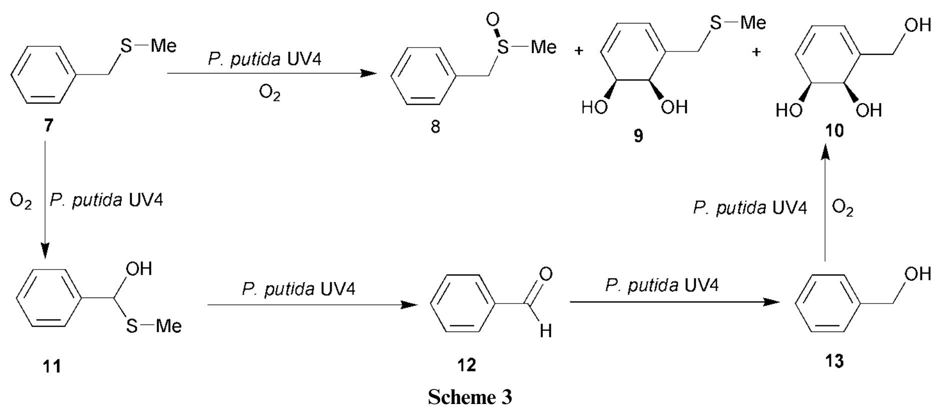
Thioacetals **1** and **4** offered the options of oxidation at either alkyl aryl/dialkyl sulfur centres or arene *cis*-dihydroxylation. As expected, the major bioproduct from thioacetal **1** was the alkyl aryl sulfoxide **2** when either the TDO (18% yield) or the NDO (23% yield) systems were used. The samples of methylsulfanylmethyl phenyl sulfoxide **2**, ($[a]_D$ +169, $CHCl_3$), separated and purified by PLC (1% MeOH in $CHCl_3$), were found to be essentially enantiopure (≥98% ee) by chiral stationary phase (CSP) HPLC. Sulfoxide **2** was assigned a (+)-(*S*)-configuration by CD spectral analysis; simple alkyl aryl sulfoxides have a +ve CD absorption in the 235–255 nm region and an (*R*)-configuration which, due to a change in Sequence Rule priorities, is equivalent to an (*S*)-configuration in sulfoxide **2**. Only a trace amount of the dialkyl sulfoxide **3** was found with *P. putida* UV4 (TDO) while *P. putida* 8859 (NDO) gave a significant yield of product **3** (18%). The samples of phenylsulfanylmethyl methyl sulfoxide **3**, purified by PLC, were found to have lower ee values, 27% ee from TDO and 75% ee from NDO, on CSP HPLC analysis. Based on a CD spectral analysis, a preference for the (−)-(*S*)-configuration was found; methyl alkyl sulfoxides of (*S*)-configuration generally have a +ve CD absorption in the 215–219 nm region. A negative CD absorption at 218 nm was reported for the (*R*)-enantiomer of sulfoxide **3**, isolated from biotransformation of thioacetal **1** using *Corynebacterium equi* IFO 3730.[30]

Methylsulfanylmethyl 2-pyridyl sulfide **4** did not show any evidence of biotransformation products when used as a substrate for *P. putida* UV4. However, with *P. putida* 8859 both the alkyl aryl sulfoxide **5** (12% yield) and the dialkyl sulfoxide **6** (9% yield) were formed as metabolites. Separation of sulfoxides **5** and **6** was carried out by PLC (1% MeOH in $CHCl_3$). The isolated methylsulfanylmethyl 2-pyridyl sulfoxide **5** ($[a]_D$ +323, $CHCl_3$) was found to be enantiopure (≥98% ee from CSP HPLC) and was assigned a (+)-(*S*)-configuration by CD spectral analysis (+ve CD absorption in the region 240 nm). The minor metabolite 2-pyridylsulfanylmethyl methyl sulfoxide **6** ($[a]_D$ −107, $CHCl_3$) had a lower ee value (73% ee from CSP HPLC) and was assumed to have a (−)-(*S*)-configuration by CD spectral analysis (+ve CD absorption in the region 215 nm). The results obtained from the biotransformation of thioacetal substrates **1** and **4** suggest that sulfoxidation of a dialkyl sulfur centre is extremely difficult with TDO as biocatalyst but is possible using NDO, albeit with reduced ee values. Sulfoxidation of the alkyl aryl sulfur centres in thioacetals **1** and **4**, using either TDO or NDO as biocatalyst, occurs in a highly stereoselective manner (≥98% ee) to furnish sulfoxides **2** and **5** with an (*S*)-configuration.

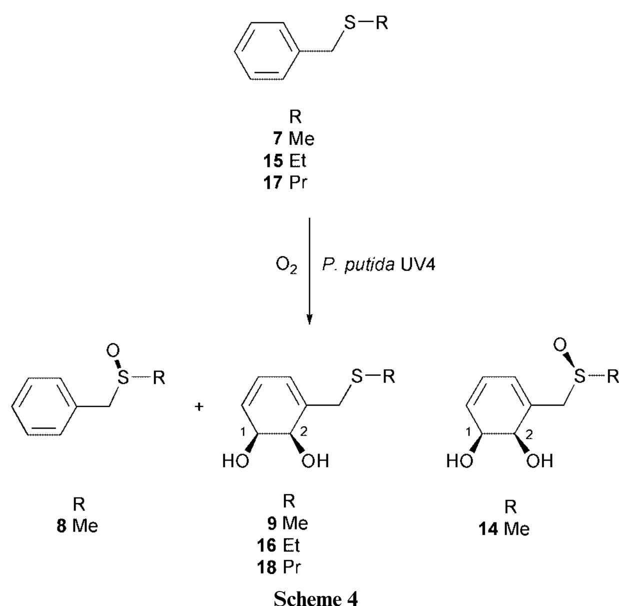
As part of an earlier report[9] focussed on the dioxygenase-catalysed trihydroxylation of monosubstituted arenes, benzyl methyl sulfide **7** was used as a substrate with intact cells of *P. putida* UV4 (Scheme 3); benzylic hydroxylation was anticipated since this position was further activated towards oxidation by the proximate sulfur atom. The isolation of the *cis*-dihydrodiol **10** of benzyl alcohol provided evidence for the latter type of monooxygenation (monohydroxylation) (Scheme 3). The hemithioacetal product **11** from benzylic hydroxylation, predicted to be unstable, was assumed to have undergone a spontaneous dealkylation yielding benzaldehyde **12**. Dehydrogenase-catalysed reduction of benzaldehyde **12** to benzyl alcohol **13**, followed by dioxygenase-catalysed *cis*-dihydroxylation gave triol **10** in low yield (2%) as the isolated end bioproduct. The object of the earlier study[9] was to find evidence of dioxygenase-catalysed benzylic hydroxylation. However, the ability of this enzyme system to catalyse arene *cis*-dihydroxylation (*e.g.* to yield compound **9**), and sulfoxidation of a dialkyl sulfide (*e.g.* to yield compound **8**), opened a new avenue for further work.

With the exception of non-aromatic conjugated polyene substrates,[31,32] virtually all of the acceptable substrates for the dioxygenase-containing *P. putida* strains available in our laboratories (*e.g.* UV4, NCIMB 8859, ML2, 9816/11) appear to require the presence of at least one benzene ring. Thus, it was considered desirable that all potential dialkyl sulfide substrates selected for the study should contain a phenyl group.

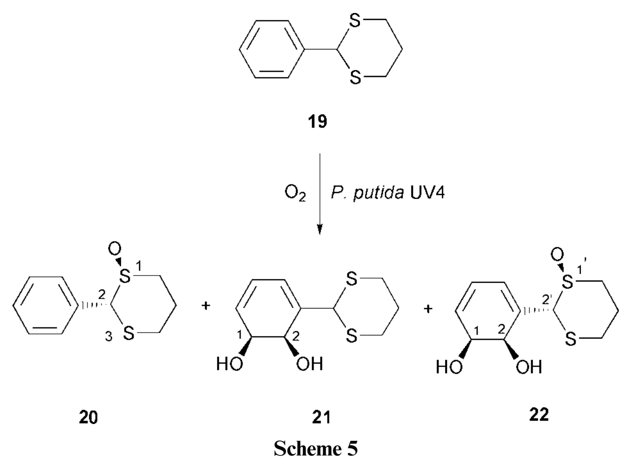
A rare example of dioxygenase-catalysed sulfoxidation of a dialkyl sulfide was earlier noticed[9] during the biotransformation of benzyl methyl sulfide **7** with *P. putida* UV4; benzyl methyl sulfoxide **8**, a minor bioproduct (8% relative yield), was isolated along with *cis*-dihydrodiol **9** as the major product (90% relative yield) (Scheme 3). In order to establish the general applicability of TDO as a biocatalyst for dialkyl sulfide oxidation, benzyl alkyl sulfides **7**, **15** and **17** and the cyclic thioacetals **19** and **23** were chosen as substrates for *P. putida* UV4 (Schemes 4–6). Unfortunately all attempts to detect and isolate the corresponding benzyl alkyl sulfoxides during the current programme were unsuccessful. TDO-Catalysed oxidation of benzyl alkyl sulfides **7**, **15** and **17** yielded only the *cis*-dihydrodiol bioproducts **9**, **16** and **18**. However, when a recombinant strain of *Escherichia coli* JM109 (pDTG141)[13] containing NDO was used in the biotransformation of the dialkyl sulfides **7** and **15**, the only metabolites isolated were the corresponding sulfoxides as NDO does not generally catalyse *cis*-dihydrodiol metabolite formation from substituted benzene substrates.[1–3] Methyl benzyl sulfoxide **8** and ethyl benzyl sulfoxide of low ee value (<1–5%) were obtained (11–20% yield).




Scheme 3

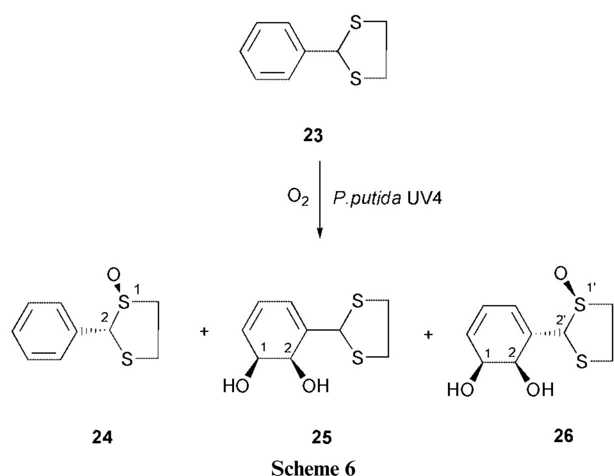



Scheme 4




Scheme 5

Addition of 2-phenyl-1,3-dithiane **19**, as a substrate for *P. putida* UV4, provided the possibility of sulfoxidation at either of the two dialkyl sulfur centres as well as *cis*-dihydroxylation of the phenyl ring. In practice, the *trans*-monosulfoxide **20** was separated, as the less polar metabolite (7% yield), by PLC from the major metabolite, *cis*-dihydrodiol **21** [18% yield, Section (b)]. A very polar minor metabolite was also isolated and identified as the *cis*-diol sulfoxide **22** [see Section (c)]. The isolated 2-phenyl-1$\lambda^4$,3-dithiane 1-oxide **20** ([$a$]$_D$ +94, $CHCl_3$) was found to be enantiopure (≥98% ee from CSP HPLC). The *trans*-structure and absolute configuration of (+)-(1*S*,2*S*)-2-phenyl-1$\lambda^4$,3-dithiane 1-oxide **20** were determined by spectral methods (NMR, MS, CD) and X-ray crystallography. The X-ray analysis showed the 1,3-dithiane ring to have adopted a chair conformation, with the phenyl ring and the oxygen atom occupying *trans*-diequatorial sites, in the solid state. The determination of absolute structure by anomalous dispersion confirmed the configuration as (+)-(1*S*,2*S*) (Fig. 1).




Scheme 6

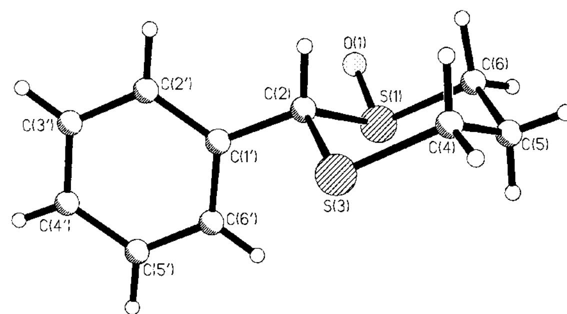



**Fig. 1** X-Ray structure of **20**.

Assuming that the enantiopure sample of 2-phenyl-1$\lambda^4$,3-dithiane 1-oxide **20** is formed only by a TDO-catalysed asymmetric oxidation process, then it follows that this enantiomer is the result of an exclusive preference for the *pro-S* lone pair on the *pro-S* sulfur atom. Sulfoxide **20** was previously synthesised in low ee (10%) by the Kagan's asymmetric oxidation procedure.[33]

The thioacetal substrate 2-phenyl-1,3-dithiolane **23** was initially found to yield two biotransformation products with *P. putida* UV4. The least polar bioproduct, separated by flash chromatography, was identified as *trans*-2-phenyl-1$\lambda^4$,3-dithiolane 1-oxide **24** (12% yield). The relative stereochemistry of compound **24** was earlier assigned as *trans* since it was the major isomer formed during MCPBA oxidation of 2-phenyl-1,3-dithiolane **23**; its $^{1}$H- and $^{13}$C-NMR spectra showed characteristic features of a *trans*-isomer.[34] CSP HPLC analysis was carried out to determine the enantiopurity of sulfoxide **24** ([$a$]$_D$ −103, $CHCl_3$; 78% ee). Fractional crystallization provided

enantiopure sulfoxide **24** ($[a]_D$ −129, $CHCl_3$, ≥98% ee). This sample of sulfoxide **24** provided confirmation of the *trans*-stereochemistry and the (1*S*,2*S*) absolute configuration through X-ray crystallographic analysis using the anomalous dispersion method (Fig. 2). An earlier attempt to obtain the

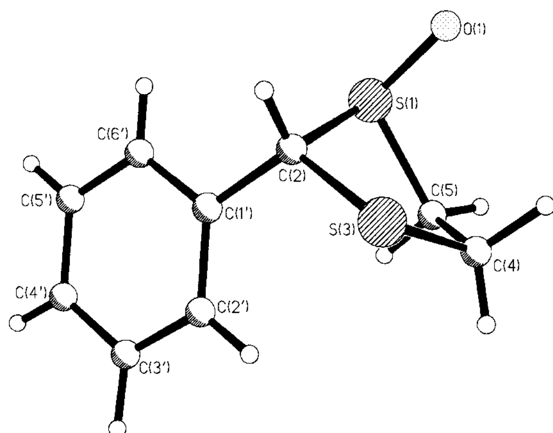



**Fig. 2** X-Ray structure of **24**.

thioacetal sulfoxide **24** by the Kagan's asymmetric oxidation procedure gave a sample with an ee value of 14%.[34]

The more polar metabolite was identified as *cis*-dihydrodiol **25** [see Section (b)]. A larger scale biotransformation of substrate **23**, using a higher cell density, yielded two bioproducts which were identified as *cis*-dihydrodiol **25** and *cis*-dihydrodiol sulfoxide **26** [see Section (c)].

### (b) Dioxygenase-catalysed dioxygenations: *cis*-dihydroxylation of phenyl groups

It is noteworthy that where the TDO enzyme is presented with a substrate containing a phenyl group, an alkyl aryl sulfur centre or a dialkylsulfur centre (*e.g.* thioacetal **1**), aryl alkyl sulfoxidation is strongly favoured. Where the choice is between oxidation of a phenyl ring or a dialkyl sulfur centre, *e.g.* in substrates **7**, **15**, **17**, **19** or **23**, *cis*-dihydroxylation of the phenyl ring was found to be either the exclusive (to yield diols **9**, **16**, **18**) or the preferred (to yield diols **21**, **25**) metabolic pathway. The *cis*-dihydrodiols **9** (35% yield), **16** (21% yield), **18** (10% yield), **21** (18% yield) and **25** (15% yield), isolated from biotransformation (*P. putida* UV4) of the corresponding sulfides (**7**, **15**, **17**) and thioacetals (**19**, **23**) respectively, displayed similar characteristics in their $^1$H-NMR spectra. Thus, the vicinal *cis*-coupling constants ($J_{1,2}$) were found to be in the range 5.9–6.2 Hz. *cis*-Dihydrodiols **9**, **16**, **18**, **21** and **25** were all found to be enantiopure (≥98% ee) by formation of either the corresponding 2-methoxy-2-(trifluoromethyl)phenylacetic acid (MTPA) esters (diols **9**, **21**, **25**) of the 4-phenyl-1,2,4-triazoline-3,5-dione adducts and/or the corresponding 2-(1-methoxyethyl)phenylboronic acid (MEPBA) boronate derivatives (diols **9**, **16**, **18**, **21**, **25**). The two methods, allied to circular dichroism (CD) spectral comparisons, allowed absolute configurations to be assigned to the *cis*-diols; these were found to be of identical configuration to all of the other *cis*-dihydrodiol metabolites from mono-substituted benzene substrates *i.e.* (1*S*). An independent confirmation of the absolute configuration of *cis*-dihydrodiol **21** was obtained by hydrogenolysis with Raney nickel to yield the *cis*-dihydrodiol derivative of toluene of known configuration.

### (c) Dioxygenase-catalysed trioxygenations: tandem *cis*-dihydroxylation–sulfoxidation of phenyl and dialkyl sulfide groups

Evidence of benzylic hydroxylation of methyl benzyl sulfide **7** had earlier been deduced from the formation of *cis*-dihydrodiol **10** (Scheme 3); this bioproduct was not obtained from dioxygenase-catalysed oxidation of the alkyl benzyl sulfides **15** and **17**. It is probable that only two of the three oxygen atoms in metabolite **10** are derived from dioxygen. The isolation of the *cis*-diol sulfoxides **14**, **22** and **26**, as metabolites from sulfide **7** and thioacetals **19** and **23** respectively, may be the result of tandem biotransformations involving initially *cis*-dihydroxylation followed by sulfoxidation. This tentative conclusion is based on a small scale (0.2 g) biotransformation of *cis*-dihydrodiol **9** with *P. putida* UV4 which gave *cis*-diol sulfoxide **14** in low yield. When a racemic sample (0.2 g) of benzyl methyl sulfoxide **8** was subjected to biotransformation with UV4, *cis*-dihydrodiol **9** was isolated as a minor metabolite (~2%) along with more than 90% of the recovered racemic substrate **8**. This observation is consistent with a minor sulfoxide reductase-catalysed deoxygenation reaction followed by a dioxygenase-catalysed *cis*-dihydroxylation.

The structure of *cis*-dihydrodiol sulfoxide metabolite **14**, isolated as a very minor metabolite from both sulfide **7** and *cis*-diol **9** (≥1%), was determined by spectroscopic methods; its absolute stereochemistry was assigned as (1*S*,2*R*,2′*S*) by direct comparison with a sample of the diastereoisomeric (1*S*,2*R*,2′*R*)-*cis*-dihydrodiol sulfoxide **27** which was analysed by X-ray crystallography [see Section (d)].

The structure and absolute stereochemistry of the *cis*-dihydrodiol sulfoxide **22** was determined by spectral (NMR, IR, CD) and X-ray crystallographic analysis. The X-ray analysis showed that in the solid state the hydroxy groups were in a *cis* relationship with the C-1 substituent pseudo-equatorial and the C-2 substituent pseudo-axial. The determination of absolute configuration by anomalous dispersion confirmed the configuration of metabolite **22** ($[a]_D$ +50, $CHCl_3$, ≥98% ee) as (1*S*,2*R*,1′*S*,2′*S*) (Fig. 3).

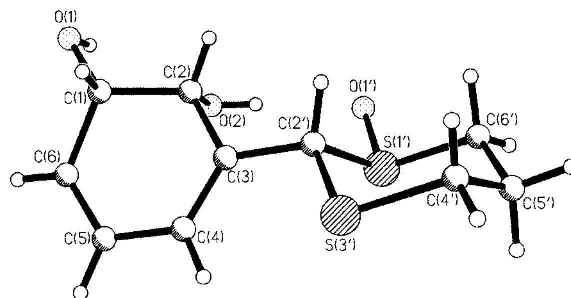



**Fig. 3** X-Ray structure of **22**.

*cis*-Dihydrodiol sulfoxide metabolite **26**, derived from 2-phenyl-1,3-dithiolane **23**, was found to be much less stable than *cis*-dihydrodiol sulfoxide **22** and could not be obtained in crystalline form. Since both *trans*-monosulfoxide metabolites **20** and **24**, and the corresponding *cis*-dihydrodiol metabolites **21** and **25**, derived from thioacetals **19** and **23** respectively, were of identical configuration, it was assumed that *cis*-dihydrodiol sulfoxide metabolite **26** had a similar configuration to metabolite **22** *i.e.*, (1*S*,2*R*,1′*S*,2′*S*).

### (d) Chemoenzymatic synthesis of *cis*-dihydrodiol sulfoxides

In order to study the selectivity of chemical oxidation of sulfur atoms in *cis*-dihydrodiols **9**, **16**, **18**, and **21**, each of the *cis*-diols was subjected to controlled oxidation with dimethyldioxirane (DMD); separable diastereoisomeric pairs of corresponding *cis*-diol sulfoxides **14** and **27**, **28** and **29**, **30** and **31** and **22** and **32** were obtained (Schemes 7 and 8). Due to the instability of *cis*-diol sulfoxide **26**, DMD sulfoxidation of diol **25** was not carried out.

X-Ray crystallographic analysis of the diol sulfoxide **27**, using the anomalous dispersion method, provided an unequivocal solution (1*S*,2*R*,2′*R*), to the assignment of its absolute

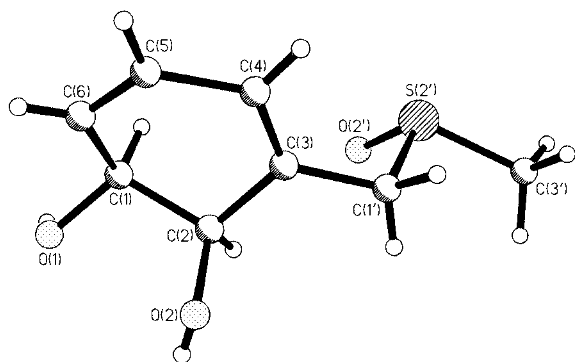
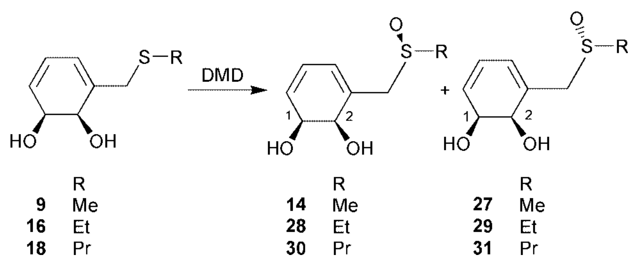
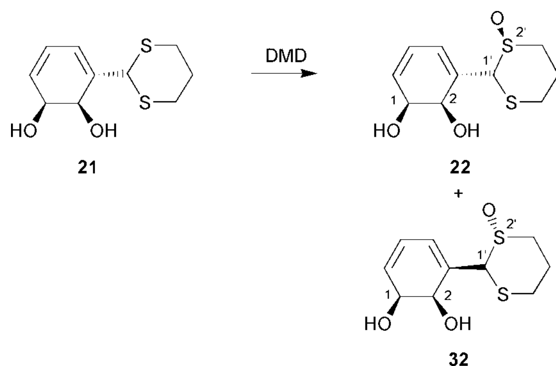



**Fig. 4** X-Ray structure of **27**.

configuration (Fig. 4). Based on a comparison of CD spectra and X-ray crystallography it was then possible to assign the absolute configurations to all of the *cis*-diol sulfoxide diastereoisomers, **14**, **28**, **29**, **30**, **31**, and **32**, resulting from the DMD oxidation. The transfer of chirality from the *cis*-dihydrodiol ring to the sulfoxide centre during sulfoxidation to yield the diol sulfoxides shown in Schemes 7 and 8 has been utilised during aromatisation studies to yield enantiopure phenolic sulfoxides. The results of the latter studies will however be reported elsewhere.




**Scheme 7**




**Scheme 8**

## Conclusion

The results obtained from this biotransformation study demonstrated that the TDO enzyme system was more reluctant to catalyse oxidation of dialkyl sulfides than alkyl aryl sulfides to the corresponding monosulfoxides. Evidence of monooxygenation (sulfoxidation) in dialkyl sulfides was however obtained using both TDO and NDO as biocatalysts for substrates having two sulfur atoms in their structure; enantiopurity of the dialkyl sulfoxide products was found to be variable. The isolation of enantiopure *cis*-dihydrodiols of identical configuration, as the major bioproducts from dialkyl sulfide substrates containing a phenyl ring, indicated that dioxygenation (ring dihydroxylation) was the preferred TDO-catalysed pathway. Formation of enantiopure diol sulfoxides **14**, **22** and **26**, from substrates **7**, **19** and **23** respectively could be rationalized through a tandem TDO-catalysed trioxygenation route. Controlled chemical oxidation of *cis*-dihydrodiol metabolites **9**, **16**, **18** and **21** with DMD produced separable diol sulfoxide diastereoisomers (**14** and **27**, **28** and **29**, **30** and **31** and **22** and **32** respectively) each possessing four stereogenic centres.

## Experimental

NMR spectra of compounds were recorded on Bruker Avance DPX-300 and DPX-500 instruments. Flash chromatography and PLC were performed on Merck Kieselgel type 60 (250–400 mesh) and $PF_{254/366}$ respectively. Merck Kieselgel $60F_{254}$ analytical plates were used for TLC. Optical rotation ($[\alpha]_D$) measurements were carried out with a Perkin-Elmer 214 polarimeter at ambient temperature (*ca.* 20 °C) and are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. CD spectra were recorded using a JASCO J-720 instrument and spectroscopic grade methanol as solvent. Enantiopurity of sulfoxides was determined by CSP HPLC using specified Chiralcel columns and hexane–propan-2-ol (9 : 1) as eluent.

Substrates were metabolized using growing cultures of the mutant strain *Pseudomonas putida* UV4 or the wild-type strain *Pseudomonas putida* NCIMB 8859, according to the reported method.[12] The bioproducts were harvested by repeated solvent extraction (EtOAc) of the sodium chloride-saturated aqueous solution containing the biotransformed material, and concentration of the combined organic extracts under reduced pressure. $^1H$ NMR spectra of the crude mixture of bioproducts, obtained from each biotransformation, were routinely recorded prior to the application of any purification procedure.

Dialkyl sulfides and thioacetals were either purchased from commercial sources (**7**, **19**) or synthesised following standard literature methods (**1**, **4**, **15**, **17**, **23**). The corresponding racemic sulfoxides were synthesized by oxidation using sodium periodate in aqueous methanol and were found to have similar physical and spectral properties to those reported in the literature.

### Methylsulfanylmethyl phenyl sulfide 1

83% yield; bp 54–58 °C/0.01 mmHg (lit.[35] bp 148–152 °C/11 mmHg); $\delta_H$ (300 MHz, $CDCl_3$) 2.22 (3 H, s, Me), 4.00 (2 H, s, $CH_2$), 7.24–7.34 (3 H, m, Ar-*H*), 7.43 (2 H, d, *J* 7.0, Ar-H).

### Methylsulfanylmethyl 2-pyridyl sulfide 4[36]

69% yield; bp 82–84 °C/0.3 mmHg; $\delta_H$ (300 MHz, $CDCl_3$) 2.24 (3 H, s, Me), 4.36 (2 H, s, $CH_2$), 6.99–7.04 (1 H, m, Ar-H), 7.21 (1 H, d, *J* 7.9, Ar-H), 7.48–7.54 (1 H, m, Ar-H), 8.46 (1 H, d, *J* 5.3, Ar-H).

### Benzyl ethyl sulfide 15

96% yield; bp 63–65 °C/0.5 mmHg (lit.[37] bp 35–36 °C/0.1 mmHg); $\delta_H$ (500 MHz, $CDCl_3$) 1.23 (3 H, t, *J* 7.4, Me), 2.43 (2 H, q, *J* 7.4, $CH_2$Me), 3.72 (2 H, s, Ar$CH_2$), 7.22–7.25 (1 H, m, Ar-H), 7.28–7.31 (4 H, m, Ar-H).

### Benzyl propyl sulfide 17

92% yield; bp 117–118 °C/15 mmHg (lit.[38] bp 112 °C/14 mmHg); $\delta_H$ (500 MHz, $CDCl_3$) 0.95 (3 H, t, *J* 7.3, Me), 1.57 (2 H, m, $CH_2$Me), 2.39 (2 H, t, *J* 7.3, $CH_2$Et), 3.70 (2 H, s, Ar$CH_2$), 7.22–7.25 (1 H, m, Ar-H), 7.28–7.31 (4 H, m, Ar-H).

### 2-Phenyl-1,3-dithiolane 23

94% yield; mp 24 °C (hexane); bp 77–79 °C/0.5 mmHg (lit.[39] bp 166 °C/20.0 mmHg); $\delta_H$ (500 MHz, $CDCl_3$) 3.32–3.34 (2 H, m, $CH_2$), 3.45–3.54 (2 H, m, $CH_2$), 5.64 (1 H, s, 2-H), 7.26–7.34 (3 H, m, Ar-H), 7.52 (2 H, m, Ar-H).

**Biotransformation of methylsulfanylmethyl phenyl sulfide 1**

**(a) *P. putida* UV4.** Biotransformation of methylsulfanylmethyl phenyl sulfide **1** (10 g, 58.8 mmol, 7 h) yielded a crude mixture of two compounds. Purification by flash chromatography (5% MeOH in $CHCl_3$) afforded unreacted sulfide (0.78 g, 8%) and *(+)-(S)-(methylsulfanylmethyl) phenyl sulfoxide* **2** as a gum (2.0 g, 18%); $[a]_D$ +169 (*c* 0.46, $CHCl_3$) (Found: $M^+$ 186.0174; $C_8H_{10}OS_2$ requires 186.0173); $\delta_H$ (500 MHz, $CDCl_3$) 2.20 (3 H, s, Me), 3.74 (1 H, d, $J_{A,B}$ 13.6, -SOC$H_A$H$_B$), 3.80 (1 H, d, $J_{B,A}$ 13.6, SOCH$_A$$H_B$), 7.53–7.55 (3 H, m, Ar-*H*), 7.72–7.74 (2 H, m, Ar-*H*); *m/z* 186 ($M^+$, 3%) and 61 (100) (≥98% ee, Chiralcel OD); CD: $\lambda$/nm 196 ($\Delta\varepsilon$ +7.4), 218 ($\Delta\varepsilon$ −22.5), 259 ($\Delta\varepsilon$ +16.6).

**(b) *P. putida* NCIMB 8859.** Biotransformation of methylsulfanylmethyl phenyl sulfide **1** (0.1 g, 0.59 mmol, 24 h) yielded a crude mixture of two metabolites. Purification by PLC (5% MeOH in $CHCl_3$) afforded *(+)-(S)-(methylsulfanylmethyl) phenyl sulfoxide* **2** (0.025 g, 23%); $[a]_D$ +168 (*c* 1.0, $CHCl_3$) (≥98% ee, Chiralcel OD) and *(−)-(S)-(phenylsulfanylmethyl) methyl sulfoxide* **3** (0.02 g, 18%) as an oil, $[a]_D$ −95 (*c* 0.82, $CHCl_3$) (75% ee, Chiralcel OJ) (Found: $M^+$ 186.0170; $C_8H_{10}OS_2$ requires 186.0173); $\delta_H$ (300 MHz, $CDCl_3$) 2.66 (3 H, s, Me), 3.98 (1 H, d, $J_{A,B}$ 13.5, SC$H_A$H$_B$), 4.15 (1 H, d, $J_{B,A}$ 13.5, SCH$_A$$H_B$), 7.30–7.40 (3 H, m, Ar-H), 7.48 (2 H, d, *J* 7.5, Ar-H); CD: $\lambda$/nm 198 ($\Delta\varepsilon$ −4.75), 219 ($\Delta\varepsilon$ +4.77) (lit.[30] CD: 218 ($\Delta\varepsilon$ −1.4) for the *R* enantiomer).

**Biotransformation of methylsulfanylmethyl 2-pyridyl sulfide 4 by *P. putida* NCIMB 8859**

Biotransformation of methylsulfanylmethyl 2-pyridyl sulfide **4** (0.1 g, 0.58 mmol, 24 h) yielded a crude mixture of two sulfoxides. Purification by PLC (1% MeOH in $CHCl_3$) afforded the less polar component *(+)-(S)-(methylsulfanylmethyl) 2-pyridyl sulfoxide* **5** (0.013 g, 12%); $[a]_D$ +323 (*c* 1.28, $CHCl_3$) (≥98% ee, Chiralcel OD) (Found: $M^+$ 187.0125; $C_7H_9NOS$ requires 187.0126); $\delta_H$ (500 MHz, $CDCl_3$) 2.28 (3 H, s, Me), 3.86 (1 H, d, $J_{A,B}$ 13.9, C$H_A$H$_B$), 4.18 (1 H, d, $J_{B,A}$ 13.9, CH$_A$$H_B$), 7.39–7.42 (1 H, m, Ar-H), 7.94–7.98 (1H, m, Ar-H), 8.04 (1 H, d, *J* 7.9, Ar-H), 8.63 (1 H, d *J* 4.3, Ar-H); CD: $\lambda$/nm 209 ($\Delta\varepsilon$ −9.9), 239 ($\Delta\varepsilon$ 5.45), 276 ($\Delta\varepsilon$ 9.8).

The more polar metabolite was identified as *(−)-(S)-(2-pyridylsulfanylmethyl) methyl sulfoxide* **6**. (0.0092 g, 9%); $[a]_D$ −107 (*c* 0.92, $CHCl_3$) (Found: $M^+$ 187.0132; $C_7H_9NOS$ requires 187.0128); $\delta_H$ (500 MHz, $CDCl_3$) 2.64 (3 H, s, Me), 4.41 (1 H, d, $J_{A,B}$ 13.2, CH$_B$$H_A$), 4.69 (1 H, d, $J_{B,A}$ 13.2, C$H_B$H$_A$), 7.06–7.09 (1 H, m, Ar-H), 7.25 (1 H, d, *J* 7.5, Ar-H), 7.53–7.57 (1 H, m, Ar-H), 8.44 (1 H, d, *J* 4.5, Ar-H); CD: $\lambda$/nm 215 ($\Delta\varepsilon$ 2.1), 247 ($\Delta\varepsilon$ 1.09), 286 ($\Delta\varepsilon$ −0.57) (73% ee, Chiralcel OD).

**Biotransformation of alkyl benzyl sulfides 7, 15 and 17 with *P. putida* UV4**

Biotransformation of sulfides **7**, **15** and **17** followed by extraction (EtOAc), purification by flash chromatography on silica gel (4% MeOH in $CHCl_3$) and recrystallization ($Et_2O$–hexane) yielded the corresponding pure *cis*-dihydrodiols **9**, **16**, **18** and the *cis*-diol sulfoxide **14**.

**(+)-*cis*-(1*S*,2*R*)-3-(Methylsulfanylmethyl)cyclohexa-3,5-diene-1,2-diol 9.** 2.52 g, 35%; mp 67 °C ($Et_2O$–hexane, decomp.); $[a]_D$ +131 (*c* 1.0, $CHCl_3$) (Found: C, 56.1; H, 7.1; $C_8H_{12}O_2S$ requires C, 55.8; H, 7.0%); $\delta_H$ (500 MHz, $CDCl_3$) 2.03 (3 H, s, Me), 2.19 (1 H, d, $J_{HO,H}$ 8.1, OH), 2.56 (1 H, d, $J_{HO,H}$ 7.2, OH), 3.27 (1 H, d, $J_{A,B}$ 13.5, CH$_A$$H_B$), 3.32 (1 H, d, $J_{A,B}$ 13.6, CH$_B$$H_A$), 4.30 (1 H, d, $J_{1,2}$ 6.0, 2-H), 4.34 (1 H, m, 1-H), 5.78 (1 H, d, $J_{4,5}$ 4.9, 4-H), 5.91 (1 H, dd, *J* 9.3 and 3.1, 6-H), 5.99 (1 H, m, 5-H); $\delta_C$ (125 MHz, $CDCl_3$) 14.52, 37.63, 68.57, 69.64, 122.01, 124.44, 129.30, 136.45; CD: $\lambda$/nm 274 ($\Delta\varepsilon$ 5.14), 238 ($\Delta\varepsilon$ 1.35), 230 ($\Delta\varepsilon$ 1.82), 209 ($\Delta\varepsilon$ −1.15).

**(+)-*cis*-(1*S*,2*R*)-3-(Ethylsulfanylmethyl)cyclohexa-3,5-diene-1,2-diol 16.** 2.54 g, 21%; mp 48 °C ($Et_2O$–hexane); $[a]_D$ +69.4 (*c* 0.5, $CHCl_3$) (Found: C, 58.0; H, 7.7; $C_9H_{14}O_2S$ requires C, 58.0; H, 7.6%) (Found: $M^+$, 186.0710; $C_9H_{14}O_2S$ requires 186.0715); $\delta_H$ (500 MHz, $CDCl_3$) 1.24 (3 H, t, *J* 7.4, Me), 2.48 (2 H, q, *J* 7.4, C$H_2$Me), 3.33 (1 H, d, $J_{A,B}$ 13.7, C$H_A$H$_B$SEt), 3.36 (1 H, d, $J_{B,A}$ 13.5, CH$_A$$H_B$SEt), 4.30 (1 H, d, $J_{2,1}$ 6.0, 2-H), 4.32 (1 H, m, 1-H), 5.78 (1 H, d, $J_{4,5}$ 5.2, 4-H), 5.89 (1 H, dd, $J_{6,5}$ 9.6, $J_{6,1}$ 3.1, 6-H), 5.95 (1 H, dd, $J_{5,6}$ 9.6, $J_{5,4}$ 5.2, 5-H); $\delta_C$ (125 MHz, $CDCl_3$) 14.69, 25.27, 35.47, 68.97, 69.95, 122.20, 124.80, 129.62, 136.85; CD: $\lambda$/nm 275 ($\Delta\varepsilon$ 6.51), 229 ($\Delta\varepsilon$ 2.28).

**(+)-*cis*-(1*S*,2*R*)-3-(Propylsulfanylmethyl)cyclohexa-3,5-diene-1,2-diol 18.** Viscous oil (1.43 g, 10%); $[a]_D$ +72.5 (*c* 0.4, $CHCl_3$) (Found: $M^+$, 200.0871; $C_{10}H_{16}O_2S$ requires 200.0871); $\delta_H$ (500 MHz, $CDCl_3$) 0.97 (3 H, t, *J* 7.3, Me), 1.55–1.63 (2 H, m, C$H_2$Me), 2.43 (2 H, t, *J* 7.2, C$H_2$Et), 3.31 (1 H, d, $J_{A,B}$ 13.5, C$H_A$H$_B$SPr), 3.35 (1 H, d, $J_{B,A}$ 13.5, CH$_A$$H_B$SPr), 4.30 (1 H, d, $J_{2,1}$ 6.1, 2-H), 4.31 (1 H, m, 1-H), 5.78 (1 H, d, $J_{4,5}$ 5.0, 4-H), 5.88 (1 H, dd, $J_{6,5}$ 9.6, $J_{6,1}$ 3.3, 6-H), 5.95 (1 H, dd, $J_{5,6}$ 9.6, $J_{5,4}$ 5.2, 5-H); $\delta_C$ (125 MHz, $CDCl_3$) 13.85, 22.85, 33.44, 35.84, 69.05, 69.95, 122.23, 124.72, 129.62, 136.90; CD: $\lambda$/nm 272 ($\Delta\varepsilon$ 2.71), 237 ($\Delta\varepsilon$ 0.41), 229 ($\Delta\varepsilon$ 0.71), 209 ($\Delta\varepsilon$ −0.38).

**(+)-*cis*-(1*S*,2*R*)-3-[(*S*)-Methylsulfinylmethyl]cyclohexa-3,5-diene-1,2-diol 14.** Viscous liquid (0.066 g, 0.8%); $[a]_D$ +71.8 (*c* 0.9, $CHCl_3$) (Found: $M^+$ − $H_2O$, 170.0402; $C_8H_{10}O_2S$ requires 170.0406); $\delta_H$ (500 MHz, $CDCl_3$) 2.58 (3 H, s, Me), 3.53 (1 H, d, $J_{A,B}$ 13.0, C$H_A$H$_B$), 3.88 (1 H, d, $J_{B,A}$ 13.0, CH$_A$$H_B$), 4.27 (1 H, d, $J_{2,1}$ 6.6, 2-H), 4.30 (1 H, m, 1-H), 6.02 (1 H, m, 4-H), 6.07 (2 H, m, 5-H, 6-H); $\delta_C$ (125 MHz, $CDCl_3$) 37.65, 57.71, 67.60, 70.03, 125.04, 126.70, 130.10, 132.18; CD: $\lambda$/nm 269 ($\Delta\varepsilon$ 7.82), 238 ($\Delta\varepsilon$ −5.98), 218 ($\Delta\varepsilon$ 1.25), 203 ($\Delta\varepsilon$ −4.76).

**Biotransformation of 2-phenyl-1,3-dithiane 19 using *P. putida* UV4**

Biotransformation of thioacetal substrate **19** followed by extraction (EtOAc), purification by flash chromatography on silica gel (4% methanol–chloroform) and recrystallization ($Et_2O$–hexane) yielded thioacetal sulfoxides **20**, *cis*-dihydrodiol **21** and the *cis*-diol sulfoxides **22**. Metabolites were eluted from the chromatography column in the sequence **20**, **21** and **22**.

**(+)-(1*S*,2*S*)-2-Phenyl-1λ$^4$,3-dithiane 1-oxide 20.** 0.639 g, 7%; mp 155–157 °C ($CHCl_3$) (lit.[33] mp 145–147 °C); $[a]_D$ +94 (*c* 1.2, $CHCl_3$) (≥98% ee, Chiralcel OD); $\delta_H$ (500 MHz, $CDCl_3$) 2.28–2.38 (1 H, m, 5-H), 2.45–2.50 (1 H, m, 5-H), 2.62–2.67 (1 H, m, 4-H), 2.70–2.77 (1 H, m, 6-H), 2.80–2.88 (1 H, m, 4-H), 3.50–3.57 (1 H, m, 6-H), 4.55 (1 H, s, 2-H), 7.26–7.45 (5 H, m, Ar-*H*), 7.72–7.74 (2 H, m, Ar-*H*); $\delta_C$ (125 MHz, $CDCl_3$) 29.52, 31.41, 54.79, 69.68, 128.75, 129.11, 129.33, 133.39; CD: $\lambda$/nm 248 ($\Delta\varepsilon$ 1.60), 227 ($\Delta\varepsilon$ 6.12), 211 ($\Delta\varepsilon$ −3.17).

**Crystal data for (1*S*,2*S*)-2-phenyl-1λ$^4$,3-dithiane 1-oxide 20 (Fig. 1).** $C_{10}H_{12}OS_2$, $M_r$ = 212.3, orthorhombic, $a$ = 5.634(2), $b$ = 10.142(4), $c$ = 18.013(7) Å, $V$ = 1029.3 (6) Å$^3$, $T$ = 300 K, Mo-Kα radiation, $\lambda$ = 0.71073 Å, space group $P2_12_12_1$, $Z$ = 4, $D_x$ = 1.37 g cm$^{-3}$, $\mu$ = 0.47 mm$^{-1}$, Siemens P3 diffractometer, $\omega$ scan, $4.5 < 2\theta < 55.0°$, measured/independent reflections: 2775/2362, direct methods solution, full matrix least squares refinement on $F_o^2$, anisotropic displacement parameters for non-hydrogen atoms, hydrogens located in difference Fourier and refined as free atoms with isotropic vibration parameters, $R1$ = 0.030 for 2117 data with $F_o > 4\sigma(F_o)$, 166 parameters, $wR2$ = 0.078 (all data), $GoF$ = 1.05, Flack parameter $x$ = 0.00(8), $\Delta\rho_{min,max}$ = −0.19/0.16 e Å$^{-3}$. CCDC reference number 171330. See http://www.rsc.org/suppdata/p1/b1/b108620k/ for crystallographic files in .cif or other electronic format.

**(+)-*cis*-(1*S*,2*R*)-3-(1′,3′-Dithian-2′-yl)cyclohexa-3,5-diene-1,2-diol 21.** 1.67 g, 18%; mp 51–53 °C ($Et_2O$–hexane); $[\alpha]_D$ +81.5 (*c* 0.7, $CHCl_3$) (Found: C, 51.7; H, 6.1; $C_{10}H_{14}O_2S_2$ requires C, 52.1; H, 6.1%); $\delta_H$ (500 MHz, $CDCl_3$) 1.84–1.93 (1 H, m, 5-H′), 2.11–2.17 (1 H, m, 5-H′), 2.82–3.01 (4 H, m, 4′-H, 3′-H), 4.29 (1 H, d, $J_{2,1}$ 6.4, 2-H), 4.33 (1 H, m, 1-H), 4.88 (1 H, s, 2′-H), 5.90 (1 H, dd, $J_{6,5}$ 9.6, $J_{6,1}$ 3.3, 6-H), 5.99 (1 H, dd, $J_{5,6}$ 9.6, $J_{5,4}$ 5.5, 5-H), 6.18 (1 H, d, $J_{4,5}$ 5.3, 4-H); $\delta_C$ (125 MHz, $CDCl_3$) 25.89, 31.87, 32.01, 49.05, 69.20, 70.10, 124.21, 124.56, 131.11, 138.77; CD: $\lambda$/nm 276 ($\Delta\varepsilon$ 3.55), 254 ($\Delta\varepsilon$ 0.94), 242 ($\Delta\varepsilon$ 2.61), 214 ($\Delta\varepsilon$ −3.05).

**(+)-*cis*-(1*S*,2*R*)-3-[(1′*S*,2′*S*)-1′-Oxo-1′λ$^4$,3′-dithian-2′-yl]-cyclohexa-3,5-diene-1,2-diol 22.** 1.19 g, 12%; mp 112 °C ($Et_2O$–acetone); $[\alpha]_D$ +50.0 (*c* 1.0, $CHCl_3$) and +150 (*c* 0.6, $H_2O$) (Found: C, 48.8; H, 5.6; $C_{10}H_{14}O_3S_2$ requires C, 48.8; H, 5.7%) (Found: $M^+$, 246.0386; $C_{10}H_{14}O_3S_2$ requires 246.0385); $\delta_H$ (500 MHz, $CDCl_3$) 2.24–2.33 (1 H, m, 5′-H), 2.48–2.53 (1 H, m, 5′-H), 2.65–2.70 (1 H, m, 4′-H), 2.77–2.86 (2 H, m, 4′-H, 6′-H), 3.52 (1 H, m, 6′-H), 4.24 (1 H, d, $J_{2,1}$ 5.5, 2-H), 4.30 (1 H, m, 1-H), 4.61 (1 H, s, 2′-H), 5.99–7.07 (2 H, m, 5-H, 6-H), 6.14 (1 H, d, $J_{4,5}$ 5.2, 4-H); $\delta_C$ (125 MHz, $CDCl_3$) 29.55, 31.26, 54.41, 65.63, 67.98, 69.27, 123.32, 125.91, 131.95, 134.33; CD: $\lambda$/nm 280 ($\Delta\varepsilon$ 4.25), 227 ($\Delta\varepsilon$ −6.37).

**Crystal data for *cis*-(1*S*,2*R*)-3-[(1′*S*,2′*S*)-1′-oxo-1′λ$^4$,3′-dithian-2′-yl]cyclohexa-3,5-diene-1,2-diol 22 (Fig. 3).** $C_{10}H_{14}O_3S_2$, $M_r$ = 246.3, monoclinic, *a* = 5.2634(7), *b* = 10.0356(14), *c* = 10.9997(15) Å, $\beta$ = 97.184(2)°, *V* = 576.5(1) Å$^3$, *T* = 153 K, Mo-Kα radiation, $\lambda$ = 0.71073 Å, space group $P2_1$, *Z* = 2, $D_x$ = 1.419 g cm$^{-3}$, colourless plates, 0.30 × 0.30 × 0.05 mm, $\mu$ = 0.446 mm$^{-1}$, Bruker SMART CCD diffractometer, $\omega$ scan, 0.3° frame, 20 s per frame, 3.7 < 2$\theta$ < 56.0°, measured/independent reflections: 6184/2396, empirical absorption correction (SADABS), direct methods solution, full matrix least squares refinement on $F_o^2$, anisotropic displacement parameters for non-hydrogen atoms, hydrogens located in difference Fourier and refined as free atoms with isotropic vibration parameters, *R*1 = 0.036 for 2238 data with $F_o > 4\sigma(F_o)$, 192 parameters, *wR*2 = 0.092 (all data), *GoF* = 1.05, Flack parameter *x* = −0.06(9), $\Delta\rho_{min,max}$ = −0.20/0.34 e Å$^{-3}$. CCDC reference number 171331. See http://www.rsc.org/suppdata/p1/b1/b108620k/ for crystallographic files in .cif or other electronic format.

### Biotransformation of 2-phenyl-1,3-dithiolane 23 using *P. putida* UV4

Biotransformation of thioacetal substrate **23** followed by extraction (EtOAc), purification by flash chromatography on silica gel (4% MeOH in $CHCl_3$) and recrystallization ($Et_2O$–hexane) yielded the corresponding pure thioacetal sulfoxide **24**, *cis*-dihydrodiol **25** and the *cis*-diol sulfoxide **26**. The bioproducts were eluted from the chromatography column in the sequence **24**, **25** and **26**.

**(−)-*trans*-(1*S*,2*S*)-2-Phenyl-1λ$^4$,3-dithiolane 1-oxide 24.** Colourless crystals (0.095 g, 3%); mp 85–89 °C (lit.[34] mp 95–96 °C, 99% ee); $[\alpha]_D$ −103 (*c.* 0.8, $CHCl_3$) (≥78% ee, Chiralcel OD); $\delta_H$ (500 MHz, $CDCl_3$) 2.88–2.93 (1 H, m, 5-H), 3.23–3.36 (1 H, m, 4-H), 3.56–3.62 (1 H, m, 4-H), 3.80–3.85 (1 H, m, 5-H), 5.40 (1 H, s, 2-H), 7.33–7.39 (3 H, m, Ar-H), 7.48 (2 H, d, *J* 6.9, Ar-H); $\delta_C$ (125 MHz, $CDCl_3$) 32.44, 53.27, 77.99, 128.51, 129.01, 133.14; CD: $\lambda$/nm 228 ($\Delta\varepsilon$ −9.43). Repeated fractional crystallization from MeOH raised the optical purity of compound **24**: $[\alpha]_D$ −129 (≥98% ee).

**Crystal data for (1*S*,2*S*)-2-phenyl-1λ$^4$,3-dithiolane 1-oxide 24 (Fig. 2).** $C_9H_{10}OS_2$, $M_r$ = 198.3, orthorhombic, *a* = 6.2383(5), *b* = 8.6358(7), *c* = 17.1061(13) Å, *V* = 921.6(1) Å$^3$, *T* = 153 K, Mo-Kα radiation, $\lambda$ = 0.71073 Å, space group $P2_12_12_1$, *Z* = 4, $D_x$ = 1.429 g cm$^{-3}$, colourless blocks, 0.40 × 0.25 × 0.20 mm, $\mu$ = 0.52 mm$^{-1}$, Bruker SMART CCD diffractometer, $\omega$ scan, 0.3° frames, 20 s per frame, 4.8 < 2$\theta$ < 56.4°, measured/independent reflections: 10088/2009, empirical absorption correction (SADABS), direct methods solution, full matrix least squares refinement on $F_o^2$, anisotropic displacement parameters for non-hydrogen atoms, hydrogens located in difference Fourier and refined as free atoms with isotropic vibration parameters, *R*1 = 0.031 for 1967 data with $F_o > 4\sigma(F_o)$, 149 parameters, *wR*2 = 0.070 (all data), *GoF* = 1.11, Flack parameter *x* = −0.07(7), $\Delta\rho_{min,max}$ = −0.30/0.38 e Å$^{-3}$. CCDC reference number 171332. See http://www.rsc.org/suppdata/p1/b1/b108620k/ for crystallographic files in .cif or other electronic format.

**(+)-*cis*-(1*S*,2*R*)-3-(1′,3′-Dithiolan-2′-yl)cyclohexa-3,5-diene-1,2-diol 25.** 0.45 g, 15%; mp 54–57 °C ($Et_2O$–hexane); $[\alpha]_D$ +32.8 (*c* 0.8, $CHCl_3$) (Found: C, 50.2; H, 5.7; $C_9H_{12}O_2S_2$ requires C, 50.0; H, 5.6%); $\delta_H$ (500 MHz, $CDCl_3$) 3.26–3.39 (4 H, m, 5′-H), 4.34 (1 H, d, $J_{2,1}$ 5.7, 2-H), 4.44 (1 H, dd, $J_{1,2}$ 5.7, $J_{1,6}$ 3.0, 1-H), 5.37 (1 H, s, 2′-H), 5.85–5.92 (2 H, m, 5-H, 6-H), 6.05 (1 H, d, $J_{4,5}$ 5.3, 4-H); $\delta_C$ (125 MHz, $CDCl_3$) 39.61, 39.78, 55.65, 67.27, 70.19, 122.55, 123.11, 132.01, 138.03; CD: $\lambda$/nm 264 ($\Delta\varepsilon$ 2.01), 215 ($\Delta\varepsilon$ −1.25).

**(+)-*cis*-(1*S*,2*R*)-3-[(1′*S*,2′*S*)-1′-Oxo-1′λ$^4$,3′-dithiolan-2′-yl]-cyclohexa-3,5-diene-1,2-diol 26.** Unstable oil (1.72 g, 8%); $[\alpha]_D$ +62.0 (*c* 1.6, $CHCl_3$) (Found: $M^+$, 232.0232; $C_9H_{12}O_3S_2$ requires 232.0228); $\delta_H$ (500 MHz, $CDCl_3$) 3.12–3.17 (1 H, m, 4′-H), 3.39–3.44 (1 H, m, 5′-H), 3.54–3.59 (1 H, m, 4′-H), 3.84–3.90 (1 H, m, 5′-H), 4.44 (1 H, d, $J_{2,1}$ 6.0, 2-H), 4.47 (1 H, m, 1-H), 5.17 (1 H, s, 2′-H), 5.94–6.02 (2 H, m, 5-H, 6-H), 6.25 (1 H, d, $J_{4,5}$ 5.3, 4-H); $\delta_C$ (125 MHz, $CDCl_3$) 32.35, 56.74, 65.69, 69.64, 72.84, 122.53, 128.66, 130.70, 133.95; CD: $\lambda$/nm 264 ($\Delta\varepsilon$ 5.33), 218 ($\Delta\varepsilon$ −1.66).

### Sulfoxidation of *cis*-dihydrodiols 9, 16, 18 and 21 using dimethyldioxirane. General procedure for the synthesis of the diol sulfoxides 14, 22, 27–32

Dimethyldioxirane, DMD, was prepared as a solution in acetone by addition of potassium peroxymonosulfate (Oxone) to a mixture of water, acetone and sodium hydrogen carbonate in accordance with the literature procedure.[40] A solution of DMD (0.08 M) was added dropwise to a stirring solution of the diol in acetone maintained at 0 °C. The progress of the reaction was constantly monitored by TLC (8% MeOH in $CHCl_3$). When all of the diol had reacted, the reaction was terminated by removal of the solvent *in vacuo* to yield a mixture (*ca*: 1 : 1) of diol sulfoxide diastereoisomers, separable by PLC (8% MeOH in $CHCl_3$).

**(+)-*cis*-(1*S*,2*R*)-3-[(*S*)-Methylsulfinylmethyl]cyclohexa-3,5-diene-1,2-diol 14 and (+)-*cis*-(1*S*,2*R*)-3-[(*R*)-methylsulfinylmethyl]cyclohexa-3,5-diene-1,2-diol 27.** Compound **14** (45% yield, $R_f$ 0.23) was found to have identical physical and spectral characteristics to the sample isolated as a metabolite of benzyl methyl sulfide **7**.

The less polar diastereoisomer **27** (45% yield, $R_f$ 0.28) was identified by spectral comparison with compound **14**; mp 123 °C (MeOH–$CHCl_3$); $[\alpha]_D$ +56.2 (*c* 2.2, MeOH) (Found: C, 50.9; H, 6.5; $C_8H_{12}O_3S$ requires C, 51.1; H, 6.4%) (Found: $M^+$, 188.0511; $C_8H_{12}O_3S$ requires 188.0507); $\delta_H$ (500 MHz, $CDCl_3$) 2.59 (3 H, s, Me), 3.25 (1 H, d, $J_{A,B}$ 13.0, $CH_AH_B$), 4.08 (1 H, d, $J_{B,A}$ 13.1, $CH_AH_B$), 4.18 (1 H, d, $J_{2,1}$ 6.0, 2-H), 4.33 (1 H, m, 1-H), 5.94 (1 H, d, $J_{4,5}$ 5.2, 4-H), 6.02 (1 H, m, 5-H), 6.07 (1 H, m, 6-H); $\delta_C$ (125 MHz, $CDCl_3$) 34.14, 54.78, 66.22, 67.81, 121.72, 126.20, 128.92, 129.81; CD: $\lambda$/nm 303 ($\Delta\varepsilon$ −0.49), 267 ($\Delta\varepsilon$ 1.49), 225 ($\Delta\varepsilon$ 0.80).

**Crystal data for *cis*-(1*S*,2*R*)-3-[(*R*)-methylsulfinylmethyl]cyclohexa-3,5-diene-1,2-diol 27 (Fig. 4).** $C_8H_{12}O_3S$, $M_r$ = 188.2, orthorhombic, $a$ = 5.326(1), $b$ = 8.844(1), $c$ = 18.602(3) Å, $V$ = 876.2(2) Å$^3$, $T$ = 153 K, Mo-Kα radiation, $\lambda$ = 0.71073 Å, space group $P2_12_12_1$, $Z$ = 4, $D_x$ = 1.427 g cm$^{-3}$, colourless blocks, 0.40 × 0.35 × 0.25 mm, $\mu$ = 0.33 mm$^{-1}$, Bruker P4 diffractometer, $\omega$ scan, $4.4 < 2\theta < 50.0°$, measured/independent reflections: 938/938, direct methods solution, full matrix least squares refinement on $F_o^2$, anisotropic displacement parameters for non-hydrogen atoms, hydrogens located in difference Fourier and refined as free atoms with isotropic vibration parameters, $R1$ = 0.036 for 843 data with $F_o > 4\sigma(F_o)$, 158 parameters, $wR2$ = 0.093 (all data), $GoF$ = 1.11, Flack parameter $x$ = −0.26(19), $\Delta\rho_{min,max}$ = −0.22/0.61 e Å$^{-3}$. CCDC reference number 171333. See http://www.rsc.org/suppdata/p1/b1/b108620k/ for crystallographic files in .cif or other electronic format.

**(+)-*cis*-(1*S*,2*R*)-3-[(*S*)-Ethylsulfinylmethyl]cyclohexa-3,5-diene-1,2-diol 28 and (+)-*cis*-(1*S*,2*R*)-3-[(*R*)-ethylsulfinylmethyl]-cyclohexa-3,5-diene-1,2-diol 29.** Compound **28** was isolated as the more polar diastereoisomer; viscous oil (45% yield, $R_f$ 0.34); $[\alpha]_D$ +187 ($c$ 0.7, MeOH) (Found: M$^+$, 202.0664; $C_9H_{14}O_3S$ requires 202.0665); $\delta_H$ (500 MHz, $CDCl_3$) 1.34 (3 H, t, $J$ 7.5, Me), 2.72–2.78 (2 H, m, C$H_2$Me), 3.58 (1 H, d, $J_{A,B}$ 12.9, SC$H_A$H$_B$), 3.80 (1 H, d, $J_{B,A}$ 12.9, SCH$_A$$H_B$), 4.26 (1 H, m, 1-H), 4.30 (1 H, d, $J_{2,1}$ 6.0, 2-H), 6.01–6.09 (3 H, m, 4-H, 5-H, 6-H); $\delta_C$ (125 MHz, $CDCl_3$) 6.93, 44.96, 54.57, 66.69, 70.11, 124.73, 125.99, 129.69, 132.57; CD: $\lambda$/nm 270 ($\Delta\varepsilon$ 6.03), 234 ($\Delta\varepsilon$ −1.13), 205 ($\Delta\varepsilon$ −2.42).

Compound **29** was isolated as the less polar diastereoisomer; viscous oil (45% yield, $R_f$ 0.40); $[\alpha]_D$ +53.1 ($c$ 0.6, MeOH) (Found: M$^+$, 202.0663; $C_9H_{14}O_3S$ requires 202.0664); $\delta_H$ (500 MHz, $CDCl_3$) 1.30 (3 H, t, $J$ 7.5, Me), 2.70 (1 H, m, C$H_A$H$_B$Me), 2.82 (1 H, m, CH$_A$$H_B$Me), 3.39 (1 H, d, $J_{A,B}$ 13.2, SC$H_A$H$_B$), 3.89 (1 H, d, $J_{B,A}$ 13.2, SCH$_A$$H_B$), 4.15 (1 H, d, $J_{2,1}$ 6.0, 2-H), 4.26 (1 H, m, 1-H), 5.94–6.05 (3 H, m, 4-H, 5-H, 6-H); $\delta_C$ (125 MHz, $CDCl_3$) 7.11, 43.90, 54.68, 67.66, 69.67, 123.74, 127.09, 130.98, 131.20; CD: $\lambda$/nm 269 ($\Delta\varepsilon$ 1.12), 242 ($\Delta\varepsilon$ −0.30), 224 ($\Delta\varepsilon$ 0.59).

**(+)-*cis*-(1*S*,2*R*)-3-[(*S*)-Propylsulfinylmethyl]cyclohexa-3,5-diene-1,2-diol 30 and (−)-*cis*-(1*S*,2*R*)-3-[(*R*)-propylsulfinylmethyl]cyclohexa-3,5-diene-1,2-diol 31.** Compound **30** was isolated as the more polar diastereoisomer; viscous oil (45% yield, $R_f$ 0.19); $[\alpha]_D$ +60.3 ($c$ 1.5, $CHCl_3$) (Found: M$^+$ − $H_2O$, 198.0714; $C_{10}H_{16}O_3S$ requires 198.0715); $\delta_H$ (500 MHz, $CDCl_3$) 1.10 (3 H, t, $J$ 7.4, Me), 1.77–1.84 (2 H, m, C$H_2$Me), 2.63 (1 H, m, C$H_A$H$_B$Et), 2.76 (1 H, m, CH$_A$$H_B$Et), 3.57 (1 H, d, $J_{A,B}$ 13.0, C$H_A$H$_B$SOPr), 3.82 (1 H, d, $J_{B,A}$ 13.0, CH$_A$$H_B$SOPr), 4.26 (1 H, dd, $J_{1,6}$ 3.8, $J_{1,2}$ 5.8, 1-H), 4.30 (1 H, d, $J_{2,1}$ 5.6, 2-H), 6.01 (1 H, m, $J_{5,4}$ 4.9, 5-H), 6.07 (1 H, d, $J_{4,5}$ 4.7, 4-H), 6.08 (1 H, m, 6-H); $\delta_C$ (125 MHz, $CDCl_3$) 13.42, 16.41, 53.42, 54.99, 66.63, 70.19, 124.82, 125.96, 129.66, 132.54; $m/z$ (EI) 198 (M$^+$ − $H_2O$, 4%), 125 (M$^+$ − $C_3H_7OS$, 55%), 107 (M$^+$ − $C_3H_9O_2S$, 100%); CD: $\lambda$/nm 270 ($\Delta\varepsilon$ 4.47), 238 ($\Delta\varepsilon$ −2.98), 220 ($\Delta\varepsilon$ 0.66).

Compound **31** was isolated as the less polar diastereoisomer; viscous oil (45% yield, $R_f$ 0.24); $[\alpha]_D$ −77.6 ($c$ 3.0, $CHCl_3$) (Found: M$^+$, 216.0818; $C_{10}H_{16}O_3S$ requires 216.0820) (Found: M$^+$ − $H_2O$, 198.0718; $C_{10}H_{14}O_2S$ requires 198.0715); $\delta_H$ (500 MHz, $CDCl_3$) 1.11 (3 H, t, $J$ 7.2, Me), 1.75–1.83 (2 H, m, C$H_2$Me), 2.59 (1 H, m, C$H_A$H$_B$Et), 2.90 (1 H, m, CH$_A$$H_B$Et), 3.32 (1 H, d, $J_{A,B}$ 13.3, C$H_A$H$_B$SOPr), 4.02 (1 H, d, $J_{B,A}$ 13.3, CH$_A$$H_B$SOPr), 4.19 (1 H, d, $J_{2,1}$ 5.8, 2-H), 4.33 (1 H, m, 1-H), 5.93 (1 H, d, $J_{4,5}$ 5.1, 4-H), 6.00 (1 H, dd, $J_{5,4}$ 5.2, $J_{5,6}$ 9.7, 5-H), 6.06 (1 H, dd, $J_{6,1}$ 3.5, $J_{6,5}$ 9.6, 6-H); $\delta_C$ (125 MHz, $CDCl_3$) 13.42, 16.45, 52.02, 54.98, 67.85, 69.58, 123.58, 127.40, 131.19, 131.34; CD: $\lambda$/nm 268 ($\Delta\varepsilon$ 0.94), 229 ($\Delta\varepsilon$ 0.33), 223 ($\Delta\varepsilon$ 0.21).

**(+)-*cis*-(1*S*,2*R*)-3-[(1′*S*,2′*S*)-1′-Oxo-1′λ$^4$,3′-dithian-2′-yl]-cyclohexa-3,5-diene-1,2-diol 22 and (−)-*cis*-(1*S*,2*R*)-3-[(1′*R*,2′*R*)-1′-oxo-1′λ$^4$,3′-dithian-2′-yl]cyclohexa-3,5-diene-1,2-diol 32.** Diol sulfoxide **22** (45% yield, $R_f$ 0.17) was found to have identical physical and spectral characteristics to the sample isolated as a metabolite of 2-phenyl-1,3-dithiane **19**.

Diol sulfoxide **32**; viscous oil (45% yield, $R_f$ 0.14); $[\alpha]_D$ −47.8 ($c$ 1.5, $CHCl_3$) (Found: M$^+$, 246.0380; $C_{10}H_{14}O_3S_2$ requires 246.0384); $\delta_H$ (500 MHz, $CDCl_3$) 2.23–2.38 (1 H, m, 5′-H), 2.47–2.51 (1 H, m, 5′-H), 2.65–2.70 (1 H, m, 4′-H), 2.75–2.85 (2 H, m, 4′-H, 6′-H), 3.49–3.53 (1 H, m, 6′-H), 4.31 (1 H, dd, $J_{1,6}$ 3.5, $J_{1,2}$ 6.1, 1-H), 4.39 (1 H, d, $J_{2,1}$ 6.1, 2-H), 4.61 (1 H, s, 2′-H), 6.03–6.08 (3 H, m, 4-H, 5-H, 6-H); $\delta_C$ (125 MHz, $CDCl_3$) 29.61, 30.84, 54.93, 66.53, 67.12, 124.39, 125.08, 130.34, 134.57; CD: $\lambda$/nm 270 ($\Delta\varepsilon$ −1.14), 230 ($\Delta\varepsilon$ 4.06).

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