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# BIOTRANSFORMATION OF ORGANIC SULFIDES. PART 5. FORMATION OF CHIRAL *para*-ALKYL BENZYL METHYL SULFOXIDES BY *HELMINTHOSPORIUM* SPECIES NRRL 4671

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ABSTRACT: The fungus *Helminthosporium* species NRRL 4671 has been used for the biotransformation of a series of *para*-alkylbenzyl sulfides with alkyl groups consisting of methyl, ethyl, n.propyl, isopropyl, n.butyl, and t.butyl. For the majority of substrates, sulfoxide formation occurred in moderate yield and with predominant (*S*) chirality at sulfur; lesser amounts of sulfone product were also obtained. For substrates with alkyl groups other than methyl, hydroxylation of the alkyl substituent at the terminal carbon atom was also observed. The latter reaction was investigated by the use of isopropylbenzene, t.butylbenzene, and (±) *para* n.butylbenzyl methyl sulfoxide as substrates. The data so obtained suggest that, during biotransformation of *para*-alkyl benzyl methyl sulfides by *Helminthosporium*, *S*-oxidation precedes carbon hydroxylation.

## INTRODUCTION

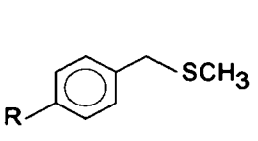
In recent years there has been a steady development in methodology for the preparation of chiral sulfoxides by asymmetric synthesis,[1,2] and sulfoxides prepared in this manner are finding increasing application as chiral synthons in organic chemistry.[3] In contrast, one of the earliest methods for the preparation of chiral sulfoxides, microbial biotransformation,[4] has not been extensively employed for preparative purposes. In spite of the success of this method in performing stereospecific asymmetric oxidation of certain prochiral sulfides,[5] and associated developments in the application of isolated oxidase enzyme methodology,[6-10] difficulties in extrapolating existing knowledge to new substrates and microorganisms have limited the applications of biotransformation for the production of preparatively useful chiral sulfoxides. To address this problem, we have undertaken a systematic study of the oxidation of prochiral sulfides by the fungus *Helminthosporium* species NRRL 4671, chosen because it is known to carry out asymmetric oxidation of a range of structurally different prochiral sulfides,[11-13] and because it typically produces little or no sulfone product,[13] ensuring that enantioselective sulfoxide formation is not significantly complicated by further enantioselective oxidation of sulfoxide to sulfone. In this paper, we present the results of biotransformations of *para*-alkyl substituted benzyl methyl sulfides. Later papers will describe the biotransformations of other *para*-substituted benzyl alkyl sulfides, and define the nature and substrate specificity of the S-oxidizing enzymes of *Helminthosporium* from a preparative standpoint.

## RESULTS AND DISCUSSION

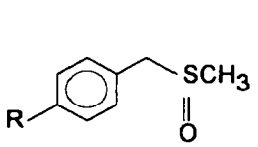
The results of the biotransformations of substrates **1** to **8** and **4a** (Figure 1) are presented in the accompanying table in terms of isolated yields, enantiomeric excesses, and predominant absolute configurations of sulfoxide products **1a** to **6a** (Figure 1) and **2c** to **6c** (Figure 2), and isolated yields of sulfone products **1b** to **6b** (Figure 1), and **2d**, **4d**, **5d**, and **9** (Figure 2).

Table. Biotransformations of sulfides **1** to **8** and sulfoxide (±)-**4a** by *Helminthosporium* species

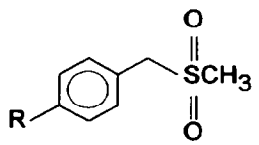
| Substrate | Products (% yield, configuration, % enantiomeric excess) | | | | |
|---|---|---|---|---|---|
| **1** | **1a** (70,*S*,52) | **1b** (3,-,-) | | | |
| **2** | **2a** (42,*S*,74) | **2b** (4,-,-) | **2c** (8,*S*,74) | **2d** (2,-,-) | |
| **3** | **3a** (45,*S*,85) | **3b** (4,-,-) | **3c** (17,*S*,95) | | |
| **4** | **4a** (60,*S*,85) | **4b** (10,-,-) | **4c** (14,*S*,>95) | **4d** (4,-,-) | **4e** (trace,$S_S$,>95$_S$) |
| **5** | **5a** (4,*S*,70) | **5b** (3,-,-) | **5c** (77,$S_S$,80$_S$) | **5d** (1,-,-) | |
| **6** | **6a** (8,*S*,26) | **6b** (2,-,-) | **6c** (58,*S*,76) | | |
| **7** | none | | | | |
| **8** | none | | | | |
| (±)-**4a** | **4a** (23,*S*,18) | **4b** (22,-,-) | **4c** (13,*S*,35) | **4d** (5,-,-) | **9** (1,-,-) |



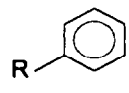

1. R = $CH_3$
2. R = $C_2H_5$
3. R = n.$C_3H_7$
4. R = n.$C_4H_9$
5. R = i.$C_3H_7$
6. R = t.$C_4H_9$




1a. R = $CH_3$
2a. R = $C_2H_5$
3a. R = n.$C_3H_7$
4a. R = n.$C_4H_9$
5a. R = i.$C_3H_7$
6a. R = t.$C_4H_9$



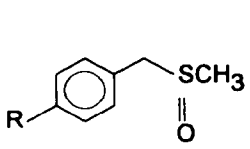

1b. R = $CH_3$
2b. R = $C_2H_5$
3b. R = n.$C_3H_7$
4b. R = n.$C_4H_9$
5b. R = i.$C_3H_7$
6b. R = t.$C_4H_9$

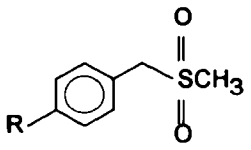


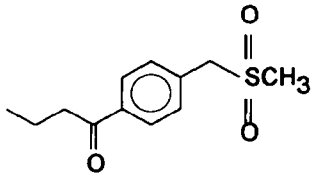

7. R = i.$C_3H_7$
8. R = t.$C_4H_9$

Figure 1. Substrates, and products of S-oxidation

The assignments of product structure relied heavily on NMR information, $^1H$ and $^{13}C$ spectral data being diagnostic of both the oxidation state at sulfur and the presence and position of hydroxyl groups in the alkyl side chains. These data, together with supporting mass spectral and (where appropriate) infra red data, are presented at length in the experimental section. The absolute configurations and enantiomeric




2c. R = $CH_2CH_2OH$ 2d. R = $CH_2CH_2OH$ 9

3c. R = $CH_2CH_2CH_2OH$ 4d. R = $CH_2CH_2CH_2CH_2OH$

4c. R = $CH_2CH_2CH_2CH_2OH$ 5d. R = $CH(CH_3)CH_2OH$

5c. R = $CH(CH_3)CH_2OH$

6c. R = $C(CH_3)_2CH_2OH$

4e. R = $CH_2CH_2CH(OH)CH_3$

Figure 2. Products of S- and C-oxidation

excesses of sulfoxide products were determined by a combination of optical rotation data and analysis of their $^1H$ NMR spectra in the presence of the chiral shift reagents (*S*)-(+)-α-methoxyphenylacetic acid (MPAA)[14] or (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine. [15] Chiral benzyl alkyl sulfoxides are known to possess opposite signs of rotation at 589 nm in ethanol and chloroform solvents, a phenomenon attributed to the presence of hydrogen bonded dimeric complexes in the latter solvent: over a wide range of alkyl groups, a correlation of configuration with rotation is conserved, namely that (*S*) enantiomers have negative rotations at 589 nm in chloroform, and positive rotations in ethanol.[2,13,16-19] In addition to this correlation being preserved throughout the present study, the configurational assignments shown in the table are strengthened by the analysis of $^1H$ NMR spectra in the presence of chiral shift reagents. Both (*S*)-(+)-MPAA and (*R*)-(-)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine gave consistent chemical shift patterns which were configurationally dependent, and which were correlated with data obtained from both (*R*)- and (*S*)-benzyl methyl sulfoxides of established configuration.[13]

The use of (*R*)-(-)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine results in enantiomeric duplication of one or both halves of the AB quartet assignable to the benzylic methylene groups of (*R*)- and (*S*)-benzyl methyl sulfoxides, as well as the sulfoxides **1a** to **6a**, **2c** to **6c**, and **4e** in a consistent and predictable manner. Conclusions reached in this way were confirmed by the use of MPAA. The latter shift reagent, in addition to producing duplication of the benzylic methylene group signals, causes the S-methyl group signals to appear as a cleanly resolved pair of singlets, with Δδ values of the order of 0.02 - 0.03 ppm. In all cases studied to date, the signal from the (*S*) enantiomer is the higher field of the two: in (*S*)-benzyl methyl sulfoxide at δ 2.466 ppm and in the (*R*) enantiomer at δ 2.482 ppm. The configurational assignments of the table are therefore proposed on the basis of both optical rotation data and the use of

two chiral NMR shift reagents. They are in full agreement with the complexation model for MPAA proposed by Buist and Marecak;[14] a detailed analysis of the use of this shift reagent for the assignment of configuration to chiral benzyl sulfoxides will appear elsewhere.[20]

It is apparent from the data presented in the table that oxidation at sulfur of *p*.alkylbenzyl methyl sulfides by *Helminthosporium* proceeds with stereoselective formation of the (*S*) sulfoxide, consistent with the known stereoselectivity of this organism in oxidation of other prochiral sulfides.[4,13] It is also apparent, however, that for substrates carrying *p*.alkyl groups other than methyl, this process is accompanied by substantial hydroxylation of the alkyl side chain at a terminal position. This mode of biotransformation is indeed the dominant one for *p*.isopropyl- and *p*.t.butylbenzyl methyl sulfides **5** and **6**, resulting in the alcohols **5c** and **6c**, respectively, as the major products. The configurations at carbon of the former product, and of the secondary alcohol centre in **4e**, produced in trace amounts (ca. 1%) from *p*.butylbenzyl methyl sulfide (**4**), have not been determined. In an attempt to study the hydroxylation reaction further, we have examined the biotransformations of *p*.isopropyl- and *p*.t.butylbenzene by *Helminthosporium* species, but in neither case were any products detected, nor were any alcohol products unaccompanied by sulfur oxidation obtained from the biotransformations of **2** to **6**. The biotransformations of **1** to **6** also produced the sulfones **1b** to **6b** in low yield, together with, in some cases, the corresponding alcohols (eg **2d**, **4d**, and **5d**), also formed in low yield.

In view of the failure of *Helminthosporium* to hydroxylate either *p*.isopropyl- or *p*.t.butylbenzene, it is inviting to assume that the hydroxylation products observed in this study are the result of further metabolism of sulfoxides, the latter being formed as the initial products of biotransformation. To examine this proposal, we have examined the biotransformation of (±)-*p*.butylbenzyl methyl sulfoxide as a representative member of the series. The results of this experiment, also presented in the table, indicate that this sulfoxide is indeed subject to hydroxylation by *Helminthosporium*, and that the products of this process are consistent with hydroxylation succeeding sulfoxidation during biotransformation of the corresponding sulfide. The alcohol **4c** produced from the racemic sulfoxide has predominant (*S*) stereochemistry at sulfur, indicating that hydroxylation is enantioselective for the (*S*) sulfoxide: the ee's of sulfoxide **4a** (85%) and alcohol **4c** (>95%) produced by biotransformation of the sulfide **4** indicate the same enantioselectivity, a phenomenon also observed for substrates **5** and **6**. The recovery of sulfoxide **4a** enriched in the (*S*) enantiomer from biotransformation of (±)-**4a** may be attributable to a degree of selectivity for the (*R*) enantiomer of **4a** in the oxidation of sulfoxide to sulfone, the major product of this particular bioconversion. However, as sulfones are typically formed in very low yields from biotransformation of sulfides by *Helminthosporium*, this selectivity, if present, cannot be a major factor in controlling the stereochemistry of any sulfoxide products thus formed. The only new product obtained from the bioconversion of (±)-**4a**, the ketone **9**, presumably results from benzylic hydroxylation of the sulfone **4b**, followed by oxidation of the resulting alcohol, a process known to be carried out by

*Helminthosporium* in low yield.[21]

Although the enantioselective oxidation of sulfoxides to sulfones is a known biotransformation,[4] enantioselective hydroxylation of sulfoxides has not hitherto been reported, being notably absent during the biotransformation of unsubstituted benzyl alkyl sulfides by *H.* species[22] or other microorganisms.[13] The role of the sulfoxide moiety in this process may be to provide a site for enzyme binding, in a manner analogous to that by which the carbonyl group directs the regiochemistry of hydroxylation during the bioconversion of steroidal and other ketones.[23] The ability of the sulfoxide group to function in this manner remains to be systematically explored.

## EXPERIMENTAL

*Apparatus, materials and methods*: melting points were determined on a Kofler heating stage. Infrared spectra were recorded with an Analect 6260FX spectrometer. The NMR spectra were recorded at 200 MHz (routine $^1H$) or 50 MHz ($^{13}C$) with a Bruker AC200 spectrometer using $CDCl_3$ as solvent and $CHCl_3$ as internal standard. Enantiomeric ratios were examined by $^1H$ NMR analysis at 500 MHz in the presence of (*S*)-(+)-α-methoxyphenylacetic acid (MPAA)[14] or (*R*)-(-)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine (Kagan reagent).[15] Optical rotations were obtained in the stated solvent at ambient temperature with a Rudolph Autopol III polarimeter. Mass spectra were obtained with a Kratos 1S instrument operating in EI mode. Thin layer chromatography was performed on Merck silica gel 60F-254 and flash column chromatography used silica gel, 230-400 mesh.

*Maintenance of microorganisms*: *Helminthosporium* species NRRL 4671 was obtained from the U.S. Department of Agriculture, Northern Regional Research Laboratories, Peoria, Ill., and was maintained on 4% malt agar slopes, grown at 27°C and stored at 4°C.

*Preparation of substrates:* substrates **7** and **8** were commercial samples. Compounds **1** to **6** were prepared by addition of the corresponding substituted benzyl chloride (0.9 eq.) to a solution of sodium thiomethoxide (1 eq.) in ethanol at room temperature, followed by refluxing of the mixture for 4h and the usual work up. All substrates gave satisfactory spectral data ($^1$HNMR, $^{13}$CNMR, ms and ir). *(±)-p.*butylbenzyl methyl sulfoxide (**4a**) was prepared from the sulfide by oxidation using sodium metaperiodate as described. [24]

*Biotransformations with* H. *species:* these are summarized in the accompanying table. Two slopes of *Helminthosporium* species NRRL 4671 were used to inoculate 15 1L Erlenmeyer flasks each containing 200 mL of an autoclaved medium composed of V-8 vegetable juice (200 mL) and calcium carbonate (3 g) per L of distilled water, adjusted to pH 7.2 prior to sterilization by the addition of 1M sodium hydroxide. The flasks were allowed to stand overnight at 27°C, then placed on a rotary shaker at 180 rpm, and growth continued for a further 72 h at 27°C. The fungus was then harvested by vacuum filtration (Buchner funnel), and resuspended in 15 1L Erlenmeyer flasks each containing 200 mL of distilled water. Substrate (1 g in 30 mL of 95% ethanol) was then distributed among the flasks, which were replaced on the rotary shaker at 180 rpm, 27°C for a further 48 h. The fungus and aqueous medium were then separated by filtration as before, the aqueous medium extracted with dichloromethane (continuous extraction, 72 h), and the fungus discarded. Concentration of the medium extract gave the crude product, which was treated as described below.

*Isolation and characterization of products:* The crude biotransformation extracts obtained as described above were examined by TLC, using ether or 10% methanol/ether as solvent, and then submitted to flash chromatography using a benzene-ether 10% stepwise gradient, followed by an ether-methanol 5% stepwise

gradient. The yields and ee values quoted in the tables refer to purified, homogeneous material, and arise from the combination of (only) homogeneous column fractions without further purification (e.g. crystallization) that could lead to changes in stereochemical enrichment values. Products were identified by a combination of NMR, mass, and infra red spectral analysis. Spectral and optical rotation data for the products obtained in this study are listed below under the appropriate substrate heading.

*Methyl* p.*methylbenzyl sulfide* (**1**). Methyl *p*.methylbenzyl sulfoxide (**1a**); mp 49-51°C; $^1$HNMR δ 2.35, 2.40 (each 3H, s, $CH_3$), 3.95 (2H, ABq, S-$CH_2$) and 7.15 (4H, s, aromatic H's) ppm; $^{13}$CNMR δ 21.2, 37.1, 60.0, 126.5, 129.7, 129.9, 138.4 ppm; ms m/z(%) 168(0.5), 152(1), 105(100), 77(10); $[\alpha]_D$ −37.1 (c = 1.8, chloroform), +40.3 (c = 0.86, ethanol), (*S*) configuration, ee 56%. Methyl *p*.methylbenzyl sulfone (**1b**); mp 129-131°C; $^1$HNMR δ 2.35, 2.72 (each 3H, s, $CH_3$), 4.2 (2H, s, S-$CH_2$), 7.25 (4H, ABq, aromatic H's); ms m/z(%) 174(0.5), 168(0.5), 152(1), 105(100), 77(10).

p.*Ethylbenzyl methyl sulfide* (**2**). *p*. Ethylbenzyl methyl sulfoxide (**2a**); oil; $^1$HNMR δ 1.20 (3H, t, $CH_3$), 2.36 (3H, s, S-$CH_3$), 2.60 (2H, q, benzylic $CH_2$), 3.90 (2H, ABq, S-$CH_2$), 7.10 (4H, s, aromatic H's) ppm; $^{13}$CNMR δ 15.4, 28.5, 37.2, 60.1, 126.7, 128.5, 129.0, 144.6 ppm; ms m/z(%) 182 (0.5), 166 (2), 119(100), 104(13), 91(21); $[\alpha]_D$ −49.6 (c = 1.82, chloroform), +65.9 (c = 0.71, ethanol), (*S*) configuration, ee 74%. *p*. Ethylbenzyl methyl sulfone (**2b**); mp 69-71°C; $^1$HNMR δ 1.22 (3H, t, $CH_3$), 2.64 (2H, q, benzylic $CH_2$), 2.72 (3H, s, S-$CH_3$), 4.18 (2H, s, S-$CH_2$), 7.15-7.35 (4H, ABq, aromatic H's) ppm; ms m/z(%) 198 (2), 133(1), 119(100), 104(10), 91(12). *p*.(2-hydroxyethyl)benzyl methyl sulfoxide (**2c**); mp 83-85°C; $^1$HNMR δ 2.1 (1H, br.s, OH), 2.42 (3H, s, S-$CH_3$), 2.80 (2H, t, benzylic $CH_2$), 3.80 (2H, t, C$H_2$OH), 3.90 (2H, ABq, S-$CH_2$), 7.15 (4H, s, aromatic H's) ppm; $^{13}$CNMR δ 37.2, 38.5, 60.0, 63.4, 127.8, 128.7, 130.2, 139.2 ppm; ms m/z(%) 182 (M-O,7), 150(1), 135 (96), 105(100), 91(15), 77(17); $[\alpha]_D$ −16.8 (c = 0.29, chloroform), +61.3 (c = 0.22, ethanol), (*S*) configuration, ee 74%. *p*.(2-hydroxyethyl)benzyl methyl sulfone (**2d**); mp 108-110°C; $^1$HNMR δ 2.70 (3H, s, S-$CH_3$), 2.80 (2H, t, benzylic $CH_2$), 3.80 (2H, t, C$H_2$OH), 4.15 (2H, s, S-$CH_2$), 7.15 (4H, s, aromatic H's) ppm; ms m/z(%) 214 (0.5), 196(6), 165(10), 119(100), 105(22), 91(40).

*Methyl* p.*propylbenzyl sulfide* (**3**). Methyl *p*.propylbenzyl sulfoxide (**3a**); oil; $^1$HNMR δ 0.90 (3H, t, $CH_3$), 1.60 (2H, m, $CH_2$), 2.42 (3H, s, S-$CH_3$), 2.56 (2H, t, benzylic $CH_2$), 3.92 (2H, ABq, S-$CH_2$), and 7.15 (4H, s, aromatic H's) ppm; $^{13}$CNMR δ 13.8, 24.2, 37.2, 37.9, 60.0, 126.5, 128.2, 129.5, 142.6 ppm; ms m/z(%) 196(0.5), 180(10), 148(4), 133(100), 104(20), 91(46); $[\alpha]_D$ −50.3 (c = 0.6, chloroform), +61.5 (c = 0.41, ethanol), (*S*) configuration, ee 85%. Methyl *p*.propylbenzyl sulfone (**3b**); mp 96-98°C; $^1$HNMR δ 0.92 (3H, t, $CH_3$), 1.60 (2H, m, $CH_2$), 2.60 (2H, t, benzylic $CH_2$), 2.75 (3H, s, S-$CH_3$), 4.20 (2H, s, S-$CH_2$), and 7.15-7.40 (4H, ABq, aromatic H's) ppm; ms m/z(%) 212(3), 180(2), 133(100), 104(20), 91(31). *p*.(3-Hydroxypropyl)benzyl methyl sulfoxide (**3c**); oil; $^1$HNMR δ 1.90 (2H, m, $CH_2$), 2.50 (3H, s, S-$CH_3$), 2.72 (2H, t, benzylic $CH_2$), 3.65 (2H, t, C$H_2$OH), 4.02 (2H, ABq, S-$CH_2$), and 7.24 (4H, s, aromatic H's) ppm; $^{13}$CNMR δ 32.0, 34.0, 37.0, 59.9, 61.5, 126.4, 129.0, 130.1, 142.4 ppm; ms m/z(%) 196(M-O,10), 180(0.5), 149(100), 131(90), 115(22), 105(28), 91(50); $[\alpha]_D$ −36.3 (c = 0.4, chloroform), +61.5 (c = 0.41, ethanol), (*S*) configuration, ee 95%.

p.*Butylbenzyl methyl sulfide* (**4**). *p*.Butylbenzyl methyl sulfoxide (**4a**); oil; $^1$HNMR δ 0.80 (3H, t, $CH_3$), 1.22 and 1.48 (each 2H, m, $CH_2$), 2.32 (3H, s, S-$CH_3$), 2.48 (2H, t, benzylic $CH_2$), 3.83 (2H, ABq, S-$CH_2$), and 7.07 (4H, s, aromatic H's) ppm; $^{13}$CNMR δ 13.9, 22.3, 33.4, 35.3, 37.2, 60.1, 126.7, 129.0, 129.9, 143.3 ppm; ms m/z(%) 210(0.5), 194(3), 180(1), 162(1), 147(100), 105(20), 91(28); $[\alpha]_D$ −47.3 (c = 2.64, chloroform), +60.4 (c = 1.04, ethanol), (*S*) configuration, ee 85%. *p*.Butylbenzyl methyl sulfone (**4b**); mp 77-79°C; $^1$HNMR δ 0.90 (3H, t, $CH_3$), 1.32 and 1.58 (each 2H, m, $CH_2$), 2.61 (2H, t, benzylic $CH_2$), 2.75 (3H, s, S-$CH_3$), 4.20 (2H, s, S-$CH_2$), and 7.15-7.35 (4H, ABq, aromatic H's) ppm; ms m/z(%) 226(1), 180(2), 147(100), 104(18), 91(26). *p*.(4-Hydroxybutyl)benzyl methyl sulfoxide (**4c**); mp 66-68°C; $^1$HNMR δ 1.45-1.75 (4H, m, $CH_2$'s), 2.40 (3H, s, S-$CH_3$), 2.60 (2H, t, benzylic $CH_2$), 3.60 (2H, t, C$H_2$OH), 3.94 (2H, ABq, S-$CH_2$) and 7.15 (4H, s, aromatic H's) ppm; $^{13}$CNMR δ 27.4, 31.8, 32.3, 35.3, 37.2, 40.6, 60.0, 62.5, 126.9, 129.0, 130.0, 142.9 ppm; ms m/z(%) 210(M-O,3), 194(1), 163(100), 145(38), 117(42), 105(48), 91(24); $[\alpha]_D$ −40.6 (c = 0.35, chloroform), +59.7 (c = 0.51, ethanol), (*S*) configuration, ee >95%. *p*.(4-Hydroxybutyl)benzyl methyl sulfone (**4d**); oil, $^1$HNMR δ 1.45-1.75 (4H, m, $CH_2$'s), 2.64 (2H, t, benzylic $CH_2$), 2.72 (3H, s, S-$CH_3$), 3.60 (2H, t, C$H_2$OH), 4.20 (2H, s, S-$CH_2$), 7.1-7.35 (4H, ABq,

aromatic H's ) ppm; $^{13}$CNMR δ 27.3, 32.2, 35.3, 40.0, 61.0, 62.5, 125.6, 129.2, 130.5, 143.6 ppm; ms m/z(%) 195(M-$C_2H_5O$,2), 179(3), 163(100), 145(33), 117(42), 104(40), 91(20). *p.*(3-Hydroxybutyl)benzyl methyl sulfoxide (**4c**); oil; $^1$HNMR δ 1.20 (3H, d, $CH_3$), 1.45-1.8 (2H, m, $CH_2$), 2.40 (3H, s, S-$CH_3$), 2.60 (2H, t, benzylic $CH_2$), 3.75(1H, m, CHOH), 3.95 (2H, ABq, S-$CH_2$); ms m/z(%) 210(M-O,2), 163(100), 145(44), 117(40), 105(45), 91(34); (*S*) configuration, ee >95%.

*Methyl* p.*isopropylbenzyl sulfide* (**5**). Methyl *p.*isopropylbenzyl sulfoxide (**5a**); oil; $^1$HNMR δ 1.26 (6H, d, $CH_3$'s), 2.45 (3H, s, S-$CH_3$), 2.90 (1H, m, benzylic CH), 3.98 (2H, ABq, S-$CH_2$), and 7.20 (4H, s, aromatic H's) ppm; $^{13}$CNMR δ 24.1, 34.2, 37.5, 60.1, 124.8, 128.1, 130.1, 143.6 ppm; ms m/z(%) 196(0.5), 180(2), 133(100), 105(27), 91(20); $[\alpha]_D$ −42.6 (c = 0.45, chloroform), +51.9 (c = 0.65, ethanol), (*S*) configuration, ee 70%. Methyl *p.*isopropylbenzyl sulfone (**5b**); oil; $^1$HNMR δ 1.25 (6H, d, $CH_3$'s), 2.76 (3H, s S-$CH_3$), 2.90 (1H, m, benzylic CH), 4.25 (2H, s, S-$CH_2$), 7.20-7.40 (4H, ABq, aromatic H's) ppm; ms m/z(%) 212(2), 196(2), 133(100), 105(29), 91(20). *p.*(1-Methyl-2-hydroxyethyl)benzyl methyl sulfoxide (**5c**); oil; $^1$HNMR δ 1.20 (3H, d, $CH_3$), 2.40 (3H, s, S-$CH_3$), 2.85 (1H, m, benzylic CH), 3.60 (2H, d, C$H_2$OH), 3.86 (2H, ABq, S-$CH_2$) and 7.18 (4H, s, aromatic H's) ppm; $^{13}$CNMR δ 17.6, 37.3, 42.2, 59.9, 66.4, 126.4, 128.2, 130.3, 145.0 ppm; ms m/z(%) 196(M-O,4), 165(4), 149(100), 119(94), 91(53); $[\alpha]_D$ +2.1 (c = 0.46, chloroform), +77.0 (c = 0.5, ethanol), ($S_S$) configuration, $ee_S$ 80%. *p.*(1-Methyl-2-hydroxyethyl)benzyl methyl sulfone (**5d**); oil; $^1$HNMR δ 1.25 (3H, d, $CH_3$), 2.75 (3H, s, S-$CH_3$), 2.96 (1H, m, benzylic CH), 3.70 (2H, d, C$H_2$OH), 4.18 (2H, s, S-$CH_2$), and 7.20-7.40 (4H, ABq, aromatic H's) ppm; ms m/z(%) 228(1), 210(0.5), 149(30), 133(82), 105(100).

p.*(t.Butyl)benzyl methyl sulfide* (**6**). *p.*(t.butyl)benzyl methyl sulfoxide (**6a**); oil; $^1$HNMR δ 1.30 (9H, s, $CH_3$'s), 2.45 (3H, s, S-$CH_3$), 3.92 (2H, ABq, S-$CH_2$), 7.1-7.4 (4H, ABq, aromatic H's) ppm; $^{13}$CNMR δ 31.2, 37.2, 59.9, 125.9, 126.0, 129.7, 146.9 ppm; ms m/z(%) 210(0.1), 194(1.5), 179(0.6), 147(100), 132(35), 117(19), 105(10), 91(10); $[\alpha]_D$ −17.1 (c = 0.35, chloroform), +20.0 (c = 0.25, ethanol), (*S*) configuration, ee 26%. *p.*(t.butyl)benzyl methyl sulfone (**6b**); 110-112°C; $^1$HNMR δ 1.30 (9H, s, $CH_3$'s), 2.75 (3H, s, S-$CH_3$), 4.20 (2H, s, S-$CH_2$), 7.25-7.5 (4H, ABq, aromatic H's) ppm; ms m/z(%) 226(2), 210(3), 179(4), 147(100), 132(32), 117(25), 105(8). *p.*(1,1-Dimethyl-2-hydroxyethyl)benzyl methyl sulfoxide (**6c**); mp 75-78°C; $^1$HNMR δ 1.30 (6H, s, $CH_3$'s), 2.41 (3H, s S-$CH_3$), 3.60 (2H, s, $CH_2$OH), 3.90 (2H, ABq, S-$CH_2$), 7.1-7.4 (4H, ABq, aromatic H's) ppm; $^{13}$CNMR δ 25.3, 37.3, 40.0, 59.7, 72.7, 126.9, 130.0, 147.2 ppm; ms m/z(%) 210(M-O,8), 179(30), 163(98), 147(47), 133(100), 117(62), 105(43), 91(39); $[\alpha]_D$−6.6 (c = 0.99, chloroform), +56.6 (c = 0.87, ethanol), (*S*) configuration, ee 76%.

i.*Propylbenzene* (**7**) Incubation of 1g of **7** with *Helminthosporium* species gave an extract (0.08 g) which consisted only of fungal natural products. No biotransformation products could be detected.

t.*Butylbenzene* (**8**) Incubation of 1g of **8** with *Helminthosporium* species gave an extract (0.07 g) which consisted only of fungal natural products. No biotransformation products could be detected.

(±)-p.*Butylbenzyl methyl sulfoxide* (**4a**). p.Butylbenzyl methyl sulfoxide (**4a**); identical with the sample described above except for $[\alpha]_D$ −10.6 (c = 0.94, chloroform), +11.7 (c = 0.98, ethanol), (*S*) configuration, ee 18%. p.Butylbenzyl methyl sulfone (**4b**); identical with the sample described above. *p.*(4-Hydroxybutyl)benzyl methyl sulfoxide (**4c**); identical with the sample described above except for $[\alpha]_D$ −16.5 (c = 1.12, chloroform), +18.3 (c = 0.98, ethanol), (*S*) configuration, ee 35%. *p.*(4-Hydroxybutyl)benzyl methyl sulfone (**4d**); identical with the sample described above. *p.*(1-oxobutyl)benzyl methyl sulfone (**9**); $^1$HNMR δ 1.04 (3H, t, $CH_3$), 1.80 (2H, m, $CH_2$), 2.80 (3H, s, S-$CH_3$), 2.96 (2H, t, $CH_2$-CO), 4.31 (2H, s, S-$CH_2$), 7.52 and 8.02 (4H, ABq, aromatic H's) ppm; ir $\upsilon_{max}$ ($cm^{-1}$) 1681; ms m/z(%) 240(0.3), 224(5), 197(62), 161(100), 133(48), 118(69).

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