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# BIOTRANSFORMATION OF ORGANIC SULFIDES. PART 6. FORMATION OF CHIRAL *para*-SUBSTITUTED BENZYL METHYL SULFOXIDES BY *HELMINTHOSPORIUM* SPECIES NRRL 4671

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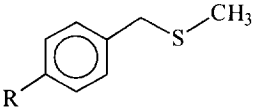
ABSTRACT: The fungus *Helminthosporium* species NRRL 4671 has been used for the biotransformation of a series of *para*-substituted benzyl sulfides with substituent groups consisting of trifluoromethyl, halo, hydroxy, methoxy, acetoxy, nitro, cyano, amino, acetamido, acyl and carboxylic acid units. In all cases, sulfoxide formation occurred in good yield and with predominant (*S*) chirality at the sulfur position. A minor amount of sulfone product was also obtained from the halo- and methoxy-substituted substrates.

## INTRODUCTION

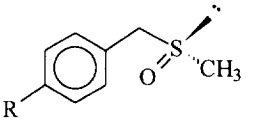
In a previous paper, we outlined the rationale for our investigation of the production of chiral sulfoxides by biotransformation of prochiral sulfides using the fungus *Helminthosporium* species NRRL 4671.[1] We have examined the formation of chiral *para* alkyl benzyl methyl sulfoxides[1] and a range of phenyl and benzyl alkyl sulfoxides.[2] In this paper we present the results of biotransformations of other *para* substituted benzyl methyl sulfides. Later papers will 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 **15** (Figure 1) are presented in the accompanying table in terms of isolated yields, enantiomeric excesses and predominant configurations of sulfoxide products **1a** to **15a**, together with isolated yields of sulfones.




**1 - 15**




**1a - 15a**

**1**, R = H; **2**, R = $CH_3$; **3**, R = F; **4**, R = Cl; **5**, R = Br; **6**, R = $OCH_3$; **7**, R = $CF_3$; **8**, R = $CO_2H$; **9**, R = $NO_2$; **10**, R = CN; **11**, R = $NH_2$; **12**, R = $NHCOCH_3$; **13**, R = OH; **14**, R = $OCOCH_3$; **15**, R = $COCH_3$

Table. Biotransformations of sulfides **1** to **15** by *Helminthosporium* species

| Substrate (para-R) | | Products | |
|---|---|---|---|
| | | Sulfoxide (% yield, configuration, % e. e.) | Sulfone (% yield) |
| **1** | H | 68, *S*, 62 | |
| **2** | $CH_3$ | 70, *S*, 52 | 3 |
| **3** | F | 82, *S*, 80 | 3 |
| **4** | Cl | 71, *S*, 90 | 12 |
| **5** | Br | 75, *S*, 88 | 10 |
| **6** | $OCH_3$ | 86, *S*, 80 | 5 |
| **7** | $CF_3$ | 68, *S*, 68 | - |
| **8** | $CO_2H$ | 21, *S*, 48 | - |
| **9** | $NO_2$ | 95, *S*, 92 | - |
| **10** | CN | 96, *S*, 98 | - |
| **11** | $NH_2$ | 62, *S*, 95 | - |
| **12** | $NHCOCH_3$ | 50, *S*, 92 | - |
| **13** | OH | 35, *S*, 80 | - |
| **14** | $OCOCH_3$ | 40, *S*, 84 | - |
| **15** | $COCH_3$ | 62, *S*, 84 | - |

Entries **1**[3] and **2**[2] are included from previous work for comparative purposes. The assignments of product structure relied heavily on NMR information, $^1H$ and $^{13}C$ spectral data being diagnostic of the oxidation state at sulfur. These, together with supporting mass spectral data, are presented at length in the experimental section. The configuration and enantiomeric excesses of sulfoxide products were determined by analysis of their $^1H$ NMR spectra in the presence of the chiral shift reagent (*S*)-(+)-α-methoxyphenylacetic acid (MPAA).[4] The use of this shift reagent for benzyl methyl sulfoxides gives consistent configurationally dependent chemical shift patterns that have been correlated with data obtained from both (*R*)- and (*S*)-benzyl methyl sulfoxides of established configuration.[4]

The 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 $\Delta\delta$ values of the order of 0.02 - 0.03 ppm. In all examples of benzyl alkyl sulfoxides studied to date,[2,4,5] the signal from the non-benzylic protons α to sulfur in the (*S*) enantiomer is the higher field: in (*S*)-benzyl methyl sulfoxide, for example, the methyl signal occurs at δ 2.466 ppm and in the (*R*) enantiomer at δ 2.482 ppm. The configurational assignments of the table are in full agreement with the complexation model proposed for MPAA interaction with sulfoxides.[4,5] In addition, chiral benzyl alkyl sulfoxides possess opposite signs of rotation at 589 nm in ethanol and chloroform solvents,[1-3,6-11] a phenomenon attributed to the formation

of dimeric complexes in the latter solvent: the presence of a hydrogen-bonding solvent is thought to disrupt this complex formation. For a wide range of non hydrogen-bonding substituents there is a correlation of configuration with rotation, namely that (*S*) enantiomers have negative rotations at 589 nm in chloroform, and positive rotations in ethanol. This correlation is preserved in the present study for products with *para* substituents which are not capable of strong dipolar interactions (eg **3a** - **6a** and **15a**), but where the substituent is capable of disrupting intermolecular sulfoxide interactions (eg **9a** or **13a**), the resulting (*S*) sulfoxide exhibits, as expected, a positive sign of rotation in both solvents.

It is apparent from the data presented in the table that oxidation at sulfur of a wide range of *para* substituted benzyl 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.[1-3,12,13] In several cases (**4a**, **5a**, and **9a-12a**), the products can be crystallized to give (*S*) sulfoxides with ≥95% optical purity. Although the enantioselective oxidation of sulfoxides to sulfones is a known biotransformation,[12] the absence of sulfone formation in most of the biotransformations listed in the table implies that the stereoselectivity of sulfoxide production lies in the enantiotopic selectivity of the enzyme responsible for sulfide oxidation. The scope of the preparative application of this enzyme in the form of a predictive model for sulfoxidation will be presented in a future publication.

## 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 $^1$H) 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 $^1$H NMR analysis at 500 MHz in the presence of 3 equivalents of (*S*)-(+)-α-methoxyphenylacetic acid (MPAA).[4] Optical rotations were obtained in the stated solvent at an 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:* with the exception of those cases detailed below, substrates were prepared by treatment of the appropriate *para* substituted benzyl chloride or bromide with 1.1 equivalents of sodium thiomethylate in ethanol. Reflux for 1-4 h, followed by conventional work up, gave the corresponding methyl thioethers in (typically) 80-90% isolated yield. All substrates prepared in this manner exhibited satisfactory spectral ($^1$H NMR, $^{13}$C NMR, mass) and other analytical data.

*4-(Methylthiomethyl)benzoic acid (**8**)*: based on a procedure by Mann,[14] a mixture of 4-(methylthiomethyl) benzonitrile (4 mL) and 10% aqueous sodium hydroxide (40 mL) was stirred and refluxed for 5 h. The mixture was then cooled, washed with ether, acidified and extracted with ether (3 x 100 mL). This extract was dried and evaporated to yield 3.8 g of white crystalline product with mp 142-144°C, $^1$H NMR δ 2.0 (3H, s), 3.73 (2H, s) and 7.38/8.08 (4H, ABq) ppm; $^{13}$C NMR δ 14.9, 38.2, 128.1, 129.0, 130.5, 144.8 and 171.9 ppm; ms m/z(%) 182(52), 135(100), 107(20).

*4-Nitrobenzyl methyl sulfide (**9**)*: a solution of sodium thiomethylate (4.3 g) in ethanol (50 mL) was added to a warm, stirred solution of 4-nitrobenzyl chloride (9.5 g) in absolute ethanol (75 mL) over a period of

90 mins. at such a rate that the initially-produced green colour was continuously dissipated. The reaction mixture was then refluxed for 1h, most of the solvent removed by evaporation and the residue was added to water and extracted with ether. The extract was washed (water), dried and evaporated to give a pale yellow oil (8.8 g), $^1$H NMR δ 2.0 (3H, s), 3.7 (2H, s) and 7.45/8.2 (4H, ABq) ppm; $^{13}$C NMR δ 15.0, 37.8, 123.7, 129.6 and 146.1 ppm; ms m/z(%) 183(100), 168(8), 136(95), 121(13), 106(27), 89(44), 78(48).

*4-Aminobenzyl methyl sulfide (11)*: concentrated hydrochloric acid (25 mL) was added in 5 mL aliquots to a stirred mixture of 4-nitrobenzyl methyl sulfide (2.5 g) and granulated tin (5 g). Ethanol (10 mL) was then added and the resulting mixture refluxed for 30 mins. The mixture was then cooled, basified with 30% aqueous sodium hydroxide, and extracted with ether (3 x 75 mL). The extract was washed with water, dried and evaporated to give a yellow oil (1.4 g), $^1$H NMR δ 2.0 (3H, s), 3.6 (2H, s) and 6.55/7.0 (4H, ABq) ppm; ms m/z(%) 153(17), 136(7), 106(100), 77(12).

*4-Acetamidobenzyl methyl sulfide (12)*: treatment of **11** with acetic anhydride/acetic acid in the usual manner, followed by conventional work-up, gave a quantitative yield of **12**, mp 135-137°C from ethyl acetate/hexane; $^1$H NMR δ 2.0 (3H, s), 2.2 (3H, s), 3.65 (2H, s) and 7.25/7.48 (4H, ABq) ppm; $^{13}$C NMR δ 14.8, 24.5, 37.7, 119.9, 129.4, 134.2, 136.8 and 166.2 ppm; ms m/z(%) 195(10), 182(3), 163(10), 148(52), 106(100), M$^+$ 195.0723, $C_{10}H_{13}NOS$ requires 195.07179.

*4-(Methylthiomethyl)phenol (13)*: based on a procedure by Miyata and Ohsuga,[15] a solution of 4-chloromethylphenyl acetate[16] (19.98 g) in ethanol (100 mL) was added to a solution of sodium thiomethylate (8.0 g) in ethanol (100 mL) and the resulting mixture refluxed for 1h. The mixture was then cooled, the bulk of the solvent removed by evaporation, and water (200 mL) was then added to the residue. This mixture was then extracted with ether (4 x 100 mL), and the extract washed with 5% aqueous KOH (2 x 100 mL). The combined aqueous washings were then acidified and extracted with ether. The final extract was dried and evaporated to yield 14.1 g (85%) of **13** as a yellow oil identical to that reported;[15] $^1$H NMR δ 1.95 (3H, s), 3.60 (2H, s) and 6.75/7.15 (4H, ABq) ppm; ms m/z(%) 154(23), 137(5), 121(8), 107(100), 95(6).

*4-(Methylthiomethyl)phenyl acetate (14)*: treatment of the phenol **13** (3 g) with acetic anhydride (3 mL) in dry pyridine (15 mL) followed by the usual work up afforded **14** in quantitative yield; oil; $^1$H NMR δ 1.95 (3H, s), 2.24 (3H, s), 3.62 (2H, s) and 7.0/7.28 (4H, ABq) ppm.

*4-(Methylthiomethyl)acetophenone (15)*: based on a procedure by Bagnell *et al.*[17] a solution nickel acetylacetonate (0.15 g) in dry benzene (6 mL) was added in aliquots of 1 mL at regular intervals over a 72 h. period to a stirred solution of 4-(methylthiomethyl)benzonitrile (2.4 g) and trimethyl aluminum (9 mL, 2M in hexanes) in dry benzene (20 mL). The mixture was then worked up by the addition of wet benzene (5 mL), followed by the careful addition of water (1.5 mL). The resulting mixture was washed (5% HCl) and the washings extracted with ether. The combined organic layers were then washed, dried and evaporated to give a pale yellow oil (1.97 g); $^1$H NMR δ 1.98 (3H, s), 2.58 (3H, s), 3.79 (2H, s), and 7.38/7.92 (4H, ABq) ppm; ms m/z(%) 180(90), 133(100), 105(48).

*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, resulting in an average of 90g (wet weight) of mycelial growth per flask. 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 another 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 the 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, unless otherwise stated, 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 and mass spectral analysis. Spectral and optical rotation data for products obtained in this study are listed below under the appropriate substrate heading.

*4-Fluorobenzyl methyl sulfide* (**3**). 4-Fluorobenzyl methyl sulfone (0.03 g) mp 101-103°C (lit.[18] mp 111.5°); $^1$H NMR δ 2.87 (3H, s), 4.23 (2H, s) and 7.05-7.45 (4H, m) ppm; ms m/z(%) 190(1), 172 (0.5), 109(100): (*S*)-4-fluorobenzyl methyl sulfoxide (**3a**, 0.82 g) mp 73-75°C (lit.[19] mp 73-75°C); $^1$H NMR δ 2.48 (3H, s), 3.93/4.0 (2H, ABq), and 7.0-7.32 (4H, m) ppm; $^{13}$C NMR δ 37.3, 59.1, 115.7/116.1, 125.6, 131.7/131.8 and 160.4/165.3 ppm; ms m/z(%) 172(1), 156(0.5), 139(0.5), 109(100); $[\alpha]_D$ +92.9 (c = 0.7, ethanol), -0.78 (c = 1.035, chloroform), ee 80%.

*4-Chlorobenzyl methyl sulfide* (**4**). 4-Chlorobenzyl methyl sulfone (0.14 g) mp 118-120°C (lit.[20] mp 120-122°C); $^1$H NMR δ 2.77 (3H, s), 4.22 (2H, s) and 7.38 (4H, s) ppm; ms m/z(%) 204/206(3.6/1.4), 172(0.4), 125/127(100/34): (*S*)-4-chlorobenzyl methyl sulfoxide (**4a**, 0.71 g), mp 108-110°C (lit.[21] mp 98.5-100°C (racemate)); $^1$H NMR δ 2.44 (3H, s), 3.89/3.93 (2H, ABq) and 7.21/7.35 (4H, ABq) ppm; $^{13}$C NMR δ 37.4, 59.2, 128.3, 129.1, 131.4 and 135.0 ppm; ms m/z(%) 188/190(1/0.4), 172(0.5), 125/127(100/34); $[\alpha]_D$ +119.3 (c = 0.62, ethanol), -8.6 (c = 0.63, chloroform), ee 90%. Crystallization from benzene/hexane gave a sample with mp 108-110°C; $[\alpha]_D$ +125.9 (c = 0.8, ethanol), -9.4 (c = 1.3, chloroform), ee ≥95%.

*4-Bromobenzyl methyl sulfide* (**5**). 4-Bromobenzyl methyl sulfone (0.15 g) mp 135-137°C; $^1$H NMR δ 2.78 (3H, s), 4.21 (2H, s) and 7.30/7.58 (4H, ABq) ppm; ms m/z(%) 248/250(5/5), 216/218(1/1), 169/171(100/98): (*S*)-4-bromobenzyl methyl sulfoxide (**5a**, 0.75 g), mp 124-126°C (lit.[22] mp 103° (racemate)); $^1$H NMR δ 2.46 (3H, s), 3.93 (2H, s) and 7.15/7.50 (4H, ABq) ppm; $^{13}$C NMR δ 37.4, 59.4, 123.8, 131.6, 131.9 and 132.2 ppm; ms m/z(%) 232/234(2/2), 216/218(2/2), 169/171(100/98); $[\alpha]_D$ +94.5 (c = 0.94, ethanol), -8.0 (c = 1.20, chloroform), ee 88%. Crystallization from benzene/hexane gave a sample with mp 128-130°C; $[\alpha]_D$ +110.2 (c = 0.63, ethanol), -8.9 (c = 1.9, chloroform), ee ≥95%.

*4-Methoxybenzyl methyl sulfide* (**6**). 4-Methoxybenzyl methyl sulfone (0.05 g) mp 107-109°C (lit.[21] mp 108-109°C); $^1$H NMR δ 2.73 (3H, s), 3.80 (3H, s), 4.18 (2H, s) and 6.95/7.35 (4H, ABq) ppm; ms m/z(%) 200(1), 184(2), 168(2), 121(100): (*S*)-4-methoxybenzyl methyl sulfoxide (**6a**, 0.87 g), mp 63-65°C (lit.[21] mp 60-61°C (racemate)); $^1$H NMR δ 2.41 (3H, s), 3.78 (3H, s), 3.92/4.09 (2H, ABq) and 6.90/7.20 (2H, ABq) ppm; $^{13}$C NMR δ 37.0, 55.2, 59.5, 114.3, 121.4, 131.1 and 159.7 ppm; ms m/z(%) 184(0.2), 168(2), 121(100); $[\alpha]_D$ +54.8 (c = 0.64, ethanol), -42.0 (c = 0.81, chloroform), ee 80%.

*4-Trifluoromethylbenzyl methyl sulfide* (**7**). (*S*)-4-Trifluoromethylbenzyl methyl sulfoxide (**7a**, 0.68 g) mp 100-102°C; $^1$H NMR δ 2.82 (3H, s), 3.96/4.0 (2H, ABq), and 7.55/7.70 (4H, ABq) ppm; $^{13}$C NMR δ 37.4, 59.2, 121.4, 125.4, 129.5 and 142.5 ppm; ms m/z(%) 222(3), 206(2), 159(100), 140(8), 109(20); $[\alpha]_D$ +84.9 (c = 1.06, ethanol), +11.3 (c = 0.84, chloroform), ee 68%.

*4-(Methylthiomethyl)benzoic acid* (**8**). The pH of the medium resulting from the biotransformation of **8** was adjusted to 4.0 with HCl prior to extraction. The product **8a** (0.23 g) obtained from chromatography was converted to the methyl ester with diazomethane to facilitate NMR shift reagent analysis. The following data were obtained for the resulting (*S*)-methyl 4(methylsulfinylmethyl)benzoate: mp 87-89°C; $^1$H NMR δ 2.45 (3H, s), 3.90 (3H, s), 3.97/4.02 (2H, ABq) and 7.47/8.04 (4H, ABq) ppm; $^{13}$C NMR δ 37.5, 52.3, 59.8, 122.0, 130.0, 130.1 and 166.6 ppm; ms m/z(%) 226(1), 210(7), 163(100); $[\alpha]_D$ +52.8 (c = 0.64, ethanol), -11.5 (c = 0.53, chloroform), ee 48%.

*4-Nitrobenzyl methyl sulfide* (**9**). (*S*)-4-Nitrobenzyl methyl sulfoxide (**9a**, 0.95 g), mp 109-111°C (lit.[22] mp 108°C (racemate)); $^1$H NMR δ 2.54 (3H, s), 4.0/4.11 (2H, ABq) and 7.51/8.37 (4H, ABq) ppm; $^{13}$C NMR δ 37.8, 59.0, 123.9, 131.0, 131.2 and 137.1 ppm; ms m/z(%) 199(6), 183(9), 136(100), 106(30), 89(40), 78(70); $[\alpha]_D$ +172.7 (c = 0.97, ethanol), +58.1 (c = 0.9, chloroform), ee 92%. Crystallization from benzene/hexane gave a sample with mp 110-112°C; $[\alpha]_D$ +177.5 (c = 1.4, ethanol), +62.6 (c = 1.66, chloroform), ee ≥95%.

*4-(Methylthiomethyl)benzonitrile* (**10**). (*S*)-4-(Methylsulfinylmethyl)benzonitrile (**10a**, 0.97 g) mp 128-129°C; $^1$H NMR δ 2.50 (3H, s), 3.94/4.04 (2H, ABq) and 7.42/7.71 (4H, ABq) ppm; $^{13}$C NMR δ 37.7, 59.3, 112.4, 118.9, 130.9, 132.5 and 135.2 ppm; ms m/z(%) 179(3), 163(3), 116(100), 89(20); $[\alpha]_D$ +186.5 (c = 0.5, ethanol), +57.8 (c = 0.9, chloroform), ee 98%. Crystallization from benzene/hexane gave a sample with a mp of 128-130°C; $[\alpha]_D$ +190.8 (c = 0.6, ethanol), +59.9 (c = 0.86, chloroform), ee ≥98%.
*4-Aminobenzyl methyl sulfide* (**11**). (*S*)-4-Aminobenzyl methyl sulfoxide (**11a**, 0.63 g); oil (lit.[21] reports mp 99-101.5°C for the racemate); $^1$H NMR δ 2.27 (3H, s), 3.68/3.81 (2H, ABq), 3.90 (2H, br.s) and 6.50/6.90 (4H, ABq) ppm; $^{13}$C NMR δ 36.6, 59.6, 114.9, 118.1, 130.7 and 146.8 ppm; ms m/z(%) 152(1), 106(100), 77(11); $[\alpha]_D$ +18.4 (c = 0.425, ethanol), -81.2 (c = 0.5, chloroform), ee 95%. A sample converted to (*S*)-4-acetamidobenzyl methyl sulfoxide by treatment with acetic anhydride in pyridine showed a mp of 170-172°C; $[\alpha]_D$ +63.1 (c = 0.49, ethanol), -20.1 (c = 0.5, chloroform), ee 98%.
*4-Acetamidobenzyl methyl sulfide* (**12**). (*S*)-4-Acetamidobenzyl methyl sulfoxide (**12a**, 0.52 g); mp 168-170°C; $^1$H NMR δ 2.15 (3H, s), 2.44 (3H, s), 3.88/3.94 (2H, ABq) and 7.20/7.50 (4H, ABq) ppm; $^{13}$C NMR δ 24.2, 37.3, 59.6, 120.2, 124.7, 130.6 139.6 and 168.5 ppm; ms m/z(%) 195(10), 163(10), 148(53), 106(100); $[\alpha]_D$ +61.9 (c = 0.83, ethanol), -14.6 (c = 0.55, chloroform), ee 92%. Crystallization from methanol/benzene gave a sample with a mp of 174-176°C; $[\alpha]_D$ +64.0 (c = 0.6, ethanol), -20.3 (c = 0.6, chloroform), ee ≥98%.
*4-(Methylthiomethyl)phenol* (**13**). (*S*)-4-(Methylsulfinylmethyl)phenol (**13a**, 0.36 g) mp 126-128°C; $^1$H NMR δ 2.49 (3H, s), 3.86/3.91 (2H, ABq) and 7.75/7.1 (4H, ABq) ppm; $^{13}$C NMR δ 36.4, 59.0, 115.5, 119.3, 130.7 and 157.1 ppm; ms m/z(%) 170(0.5), 154(4), 107(100), 106(86), 78(61); $[\alpha]_D$ +45.2 (c = 0.46, ethanol), +31.1 (c = 0.81, chloroform), ee 80%.
*4-(Methylthiomethyl)phenyl acetate* (**14**). (*S*)-4-(Methylsulfinylmethyl)phenol (**13a**, 0.42 g), identical with the sample of **13a** described above except for $[\alpha]_D$ +52.1 (c = 0.4, ethanol), +33.1 (c = 0.81, chloroform), ee 84%.
*4-(Methylthiomethyl)acetophenone* (**15**). (*S*)-4-(Methylsulfinylmethyl)acetophenone (0.63 g) was obtained contaminated with ca. 10% of 1-[4-(methylsulfinylmethyl)phenyl]ethanol. This mixture, inseparable by chromatography, was converted by Jones' oxidation to a homogeneous sample of (*S*)-4-(methylsulfinylmethyl)acetophenone as follows: a sample (100 mg) was dissolved in acetone (5 mL), the solution cooled to 0°C and stirred during the dropwise addition of Jones' reagent until the red colour persisted, after which the mixture was stirred for an additonal 5 mins at 0°C. Excess reagent was destroyed by the addition of 2-propanol, and water (20 mL) then added and the resulting mixture extracted with ether. The ether extract was dried and evaporated to give **15a** (92 mg); mp 85-88°C; $^1$H NMR δ 2.46 (3H, s), 2.59 (3H, s), 4.0 (2H, s) and 7.4/7.9 (4H, ABq) ppm; $^{13}$C NMR δ 26.6, 37.5, 59.6, 128.6, 130.3, 130.6, 134.9 and 197.7 ppm; ms m/z(%) 212(2), 196(3), 180(6), 133(100), 105(68); $[\alpha]_D$ +89.75 (c = 0.4, ethanol), -13.8 (c = 0.3, chloroform), ee 84%.

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