



Diastereoselective oxidation of menthyl arenesulfenates to sulfinates and access to enantioenriched aryl methyl sulfoxides

Matthieu Hamel, Michel Vazeux, Mihaela Gulea

► To cite this version:

Matthieu Hamel, Michel Vazeux, Mihaela Gulea. Diastereoselective oxidation of menthyl arenesulfenates to sulfinates and access to enantioenriched aryl methyl sulfoxides. Chemical Papers, 2021, 75 (11), pp.6137-6143. 10.1007/s11696-021-01759-9 . cea-03334207

HAL Id: cea-03334207

<https://cea.hal.science/cea-03334207>

Submitted on 3 Sep 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Diastereoselective oxidation of menthyl arenesulfenates to sulfinates and access to enantioenriched aryl methyl sulfoxides

Matthieu Hamel^{a,b*}, Michel Vazeux^a, Mihaela Gulea^{a,c}

^a Normandie University, ENSICAEN, UNICAEN, CNRS, Laboratoire de Chimie Moléculaire et Thioorganique, 14000 Caen, France

^b Current position: Université Paris-Saclay, CEA, List, F-91120 Palaiseau, France

^c Current position: Laboratoire d'Innovation Thérapeutique, UMR7200, Université de Strasbourg, CNRS, Faculté de Pharmacie, 74, route du Rhin, 67401 Illkirch-Graffenstaden, France

matthieu.hamel@cea.fr; ORCID 0000-0002-3499-3966 (MH), 0000-0002-2945-0078 (MG)

Keywords: Sulfenate ester; sulfinate ester; sulfoxide; diastereoselective oxidation

Abstract: Three aryl methyl sulfoxides were prepared via the following sequence: synthesis of the menthyl arenesulfenate from the corresponding thiol, diastereoselective oxidation leading to the sulfinate, then reaction with a Grignard reagent. The aryl moiety was substituted with a methyl ester on the ortho position or a nitro group on the ortho or the para position. The sulfenate esters were obtained in **fair** to excellent yield (42-

Four different oxidizing agents were tested to obtain the corresponding sulfinate esters with diastereomeric excesses (de) ranging from 10 to 48%. After separation of the diastereomers and reaction with methyl Grignard **reagent**, two enantiopure sulfoxides, and one enantioenriched sulfoxide (32% ee) were obtained.

Introduction

The interest of tri-coordinated sulfur derivatives and especially sulfoxides has successfully mutated from purely academic research to synthetic applications these last decades (Wojaczyńska and Wojaczyński 2010; Otocka et al. 2017; Wojaczyńska and Wojaczyński 2020). This success is mainly due to the discovery in the 1980s of the use of sulfoxides as efficient chiral auxiliaries for asymmetric synthesis. For example, enantiopure sulfoxides have found many applications in chiral induction (Fernández and Khier 2003), asymmetric catalysis (Pellissier 2006; Han et al. 2018), and drug design, with the well-known Esomeprazole or its derivatives (Cotton et al. 2000; Bentley 2005; O'Mahony et al. 2011), **Sulforaphane and its analogs** (Kielbasiński et al. 2014).

Some years ago, we developed an innovative access to enantiopure *ortho*-phosphorylated phenylsulfoxides, by using, as the key step, an asymmetric oxidation of sulfenates to sulfinates (Hamel et al. 2005; Abrunhosa et al. 2005). *ortho*-Phosphorylated phenylsulfinate esters have been extensively studied by the groups of Drabowicz and Mikołajczyk, and such structures have found applications as mono- or bidentate ligands for the preparation of cisplatin derivatives (Laforgia et al. 2004, 2005; Mauger et al. 2000; Hamel et al. 2013). In this work, we demonstrated the potential of this approach by its extension to other arenesulfenate substrates, bearing an electron-withdrawing group (i.e. nitro or carboxylic ester) in the *ortho* or *para* position of the aryl moiety.

Materials and Methods

Reactions were carried out under nitrogen atmosphere. THF was purified with a PURESOLV™ apparatus developed by Innovative Technology Inc. Triethylamine (Et₃N) was distilled over calcium hydride (CaH₂). Carbon tetrachloride CCl₄ was distilled over phosphorus pentoxide (P₂O₅) and stored over CaCl₂ under a nitrogen atmosphere. The synthesis of methyl thiosalicylate was performed according to a published procedure (yield 83%; lit. 97% as the crude material (Hamel et al. 2005)).

NMR spectra were recorded in deuterated chloroform (CDCl₃), unless otherwise stated on either a 250 MHz or 400 MHz NMR spectrometer. Chemical shifts δ were indicated in ppm using tetramethylsilane (TMS) as the internal standard. ¹³C {¹H} NMR spectra were recorded at 62.9 or 100.6 MHz. Mass spectra were obtained on a GC/MS Saturn 2000 or on a Waters QTOF micro. Optical rotation values were measured on a Perkin–Elmer 241 automatic polarimeter; specific rotation and concentration are given in deg cm³ g⁻¹ dm⁻¹ and g cm⁻³, respectively. IR spectra were recorded with a Perkin–Elmer 16 PC FT-IR instrument. Satisfactory analytical data were obtained using a THERMOQUEST NA 2500 instrument. Thin layer chromatography (TLC) was performed on silica gel 60 F₂₅₄, with UV detection or potassium permanganate solution (5% aqueous) staining. Flash chromatography was achieved on silica gel columns (40 – 63 μ m) using nitrogen pressure.

General procedure for the synthesis of sulfenate esters 1a-c.

Sulfonyl chloride (1.3 equiv, 9.5 mmol) was slowly added to a previously stirred solution of arenethiol (1 equiv, 7.3 mmol) in dichloromethane (20 mL). The resulting solution was stirred for 30 min at room temperature. After evacuation of the solvent and gases, tetrahydrofuran (THF, 25 mL) was added followed by (–)-menthol (1 equiv, 7.3 mmol) and trifluoroacetic anhydride (0.1 equiv, 0.73 mmol). After cooling to –78 °C, triethylamine (2 equiv., 14.6 mmol) was added. The reaction mixture was allowed to reach room temperature, stirred for one hour and then hydrolyzed with a solution of sulphuric acid (H₂SO₄, 5% aqueous). The aqueous layer was extracted with diethyl ether. The combined extracts were washed with a 5% solution of potassium carbonate (K₂CO₃) followed by brine, dried over magnesium sulfate (MgSO₄) and concentrated. The resulting oil was purified by silica gel chromatography.

Typical oxidation procedure for the synthesis of sulfinate esters **2a-c**.

With *m*CPBA

Sulfenyl ester **1** (1 equiv, 0.5 mmol) was oxidized by the addition of *meta*-chloroperoxybenzoic acid (*m*CPBA, 1 equiv, 0.5 mmol) in CH₂Cl₂ at –78 °C, after which the reaction was allowed to reach room temperature. The solvent was evaporated and the crude sulfinate **2** directly purified by silica gel chromatography.

With NBS/H₂O

N-Bromosuccinimide (NBS, 1 equiv., 1 mmol) was added portionwise to a stirred solution of menthyl sulfenyl ester **1** (1 equiv., 1 mmol) in a mixture of acetonitrile and water 2:1. The concentration of sulfenyl ester was ca. 50 mM. After addition of all the NBS, stirring was continued for 2 h and the mixture was quenched by adding a solution of H₂SO₄ (5% aqueous). The aqueous layer was extracted three times with dichloromethane. The organic layer was successively washed out with a solution of potassium carbonate (5% aqueous) and sodium thiosulfate (5% aqueous) in water. After drying and evaporation of the organic solvent, the crude extract, whose purity was usually satisfactory as shown by the NMR spectrum, was purified on a silica gel column with pentane–ethyl acetate as the eluent to obtain menthyl sulfinate **2**.

With (+)- or (–)-(8,8-dichlorocamphorylsulfonyl)oxaziridine

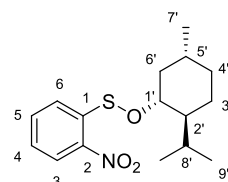
The chiral (8,8-dichlorocamphorylsulfonyl)oxaziridine (1 equiv, 0.5 mmol) was added portionwise to a stirred solution of sulfenyl ester **1** (1 equiv, 0.5 mmol) in carbon tetrachloride under a nitrogen atmosphere. After complete conversion, the solvent was evaporated and the residue dissolved in pentane. The mixture was filtered and washed once with pentane. The sulfinate was further purified on silica gel chromatography when necessary.

Grignard reaction with sulfinate esters

Methyl magnesium bromide (MeMgBr, 1.1 equiv, 1.21 mmol) was added dropwise to a stirred solution of menthyl sulfinate **2a-c** (1 equiv, 1 mmol) in 10 mL of diethyl ether at 0 °C. The resulting

mixture was stirred for 1 h at room temperature, after which 10 mL of a 5% aqueous solution of sulphuric acid was added and the aqueous layer extracted with diethyl ether. The organic extracts were washed with a solution of potassium carbonate (5% aqueous) followed by brine, dried over MgSO₄, filtered, evaporated and the mixture was further purified on silica gel chromatography, yielding **3a-c**. No scale-up experiment was performed in this study.

Numerical identifications of carbon atoms for compounds listed below are arbitrary and given only for helping the description of NMR spectra, e.g. with compound **1b**.



(–)-Menthyl 2-(methoxycarbonyl)benzenesulfonate **1a**. 78% yield; *R*_f 0.63 (pentane/ethyl acetate 90:10). White solid; mp 69 °C; [α]_D²⁰ –53.9 (c 0.9 in CHCl₃); ¹H NMR (250 MHz, δ): 7.97 (dd, 1H, ³*J* = 7.8, ⁴*J* = 1.3, H₆), 7.79 (d, 1H, ³*J* = 8.2, H₃), 7.54 (dt, 1H, ³*J* = 7.2, ⁴*J* = 1.4, H₄), 7.14 (dt, 1H, ³*J* = 7.8, ⁴*J* = 1.0, H₅), 3.92 (s, 3H, CH₃), 3.54 (dt, ³*J* = 10.6, ³*J* = 4.1, H_{1'}), 2.42 – 2.48 (m, 1H, H_{6'}), 2.27 – 2.41 (m, 1H, H_{3'}), 1.61 – 1.72 (m, 2H, H_{3'}, H_{5'}), 1.41 – 1.58 (m, 1H, H_{4'}), 1.23 – 1.40 (m, 2H, H_{4'}, H_{6'}), 1.01 – 1.14 (m, 1H, H_{8'}), 0.97 (d, 3H, ³*J* = 7.0, H_{7'}), 0.90 – 0.97 (m, 1H, H_{3'}), 0.88 (d, 6H, ³*J* = 6.4, H_{9'}); ¹³C NMR (62.9 MHz, δ): 167.4 (C=O), 151.2 (C₂), 132.7 (C₄), 130.3 (C₆), 123.3 (C₃), 121.3 (C₅), 121.0 (C_{1'}), 86.6 (C_{1'}), 52.4 (CH₃O), 49.0 (C_{2'}), 41.0 (C_{6'}), 34.3 (C_{4'}), 31.9 (C_{5'}), 25.6 (C_{8'}), 23.3 (C_{3'}), 22.2 (C_{7'}), 21.1 (C_{9'}), 16.1 (C_{9'}); IR (KBr) ν = 1690 (C=O st), 757; EIMS (*m/z* (%)): 322 (1) [*M*⁺]; 184 (85), 167 (26), 152 (100), 83 (33), 69 (15), 55 (30), 41 (15), Anal. calcd. for C₁₈H₂₆O₃S: C 67.04, H 8.13, S 9.94, found: C 66.47, H 8.20, S 10.47.

(–)-Menthyl 2-nitrobenzenesulfonate **1b**; 82% yield; *R*_f 0.74 (pentane/ethyl acetate 90:10). Yellow solid; mp 91 °C; [α]_D²⁰ –17.0 (c 1 in CHCl₃); ¹H NMR (400 MHz, δ): 8.28 (dd, 1H, ³*J* = 8.4, ⁴*J* = 1.3, H₃), 7.90 (dd, 1H, ³*J* = 8.2, ⁴*J* = 1.0, H₆), 7.66 (dt, 1H, ³*J* = 7.1, ⁴*J* = 1.3, H₅), 7.26 (dt, 1H, ³*J* = 7.3, ⁴*J* = 1.1, H₄), 3.61 (dt, 1H, ³*J* = 10.7, ³*J* = 4.2, H_{1'}), 2.40 (ddd, 1H, ³*J* = 7.0, ³*J* = 6.9, ⁴*J* = 2.7, H_{6'}), 2.25 – 2.28 (m, 1H, H_{3'}), 1.64 – 1.72 (m, 2H, H_{3'}, H_{5'}), 1.46 – 1.52 (m, 2H, H_{2'}, H_{4'}), 1.30 – 1.42 (m, 2H, H_{4'}, H_{6'}), 1.06 – 1.14 (m, 1H, H_{8'}), 0.99 (d, 3H, ³*J* = 7.0, H_{7'}), 0.90 (d, 3H, ³*J* = 6.5, H_{9'}), 0.88 (d, 3H, ³*J* = 6.9, H_{9'}); ¹³C NMR (62.9 MHz, δ): 148.0 (C₂), 134.1 (C_{1'}), 134.0 (C₄), 125.1 (C₅), 124.3 (C₆), 123.1 (C₃), 87.0 (C_{1'}), 49.0 (C_{2'}), 41.0 (C_{6'}), 34.2 (C_{4'}), 31.8 (C_{5'}), 25.7 (C_{8'}), 23.3 (C_{3'}), 22.1 (C_{7'}), 21.0 (C_{9'}), 16.1 (C_{9'}); IR (KBr) ν = 1504 (NO₂), 734; EIMS (*m/z* (%)): 332 (100) [*M* + Na]⁺, 194 (32); HRMS (ESI, *m/z*): [*M* + Na]⁺ calcd for C₁₆H₂₃NO₃NaS: 332.1296, found 332.1315; Anal. calcd. for C₁₆H₂₃NO₃S: C 62.11, H 7.50; found C 62.03, H 7.99.

(–)-Menthyl 4-nitrobenzenesulfonate **1c**; 42% yield; *R*_f 0.78 (pentane/ethyl acetate 90:10). Yellow solid; mp 70 °C; [α]_D²⁰ –162.3 (c 1.15 in CHCl₃); ¹H NMR (400 MHz, δ): 8.18 (dt, 2H, ³*J* = 9.0, ⁴*J* = 2.0, H₃), 7.31 (dt, 2H, ³*J* = 9.0, ⁴*J* = 1.9, H₂), 3.53 (dt, 1H, ³*J* = 10.7, ³*J* = 4.3, H_{1'}), 2.22 – 2.37 (m, 2H, H_{3'}, H_{6'}), 1.62 – 1.71 (m, 2H, H_{4'}, H_{5'}), 1.30 – 1.49 (m, 2H, H_{2'}, H_{3'}), 0.97 (d, 3H, ³*J* = 7.0, H_{7'}), 0.94 – 1.07 (m, 2H, H_{6'}, H_{8'}), 0.91 (d, 3H, ³*J* = 6.6, H_{9'}), 0.80 – 0.87 (m, 1H, H_{4'}), 0.82 (d, 3H, ³*J* = 7.0, H_{9'}); ¹³C NMR (62.9 MHz,

δ): 151.9 (C₄), 144.1 (C₁), 123.0 (C₆), 119.4 (C₅), 87.9 (C_{1'}), 47.8 (C_{2'}), 39.9 (C_{6'}), 33.0 (C_{4'}), 30.8 (C_{5'}), 24.5 (C_{8'}), 22.2 (C_{3'}), 21.1 (C_{7'}), 20.0 (C_{9'}), 15.0 (C_{9'}); IR (KBr) ν = 1576, 1507 (NO₂), 1337; HRMS (ESI, m/z): [M + Na]⁺ calcd for C₁₆H₂₃NO₃NaS: calcd 332.1296, found 332.1303.

(-)-Menthyl (S)-2-(methoxycarbonyl)benzenesulfinate (**S-2a**; 68% yield; R_f 0.3 (pentane/diethyl ether 70:30). White solid; mp 146 °C; [α]_D²⁰ -360.0 (c 0.6, CHCl₃); Lit. (Klunder and Sharpless 1987): -348.6 (c 1.18, acetone); ¹H NMR (400 MHz, δ): 8.26 (dd, 1H, ³J = 8.0, ⁴J = 1.2, H₆), 7.99 (dd, 1H, ³J = 7.6, ⁴J = 1.2, H₃), 7.71 (dt, 1H, ³J = 7.0, ⁴J = 1.2, H₄), 7.54 (dt, 1H, ³J = 7.1, ⁴J = 1.2, H₅), 4.08 (dt, 1H, ³J = 10.8, ³J = 4.4, H_{1'}), 3.91 (s, 3H, CH₃), 2.28 – 2.31 (m, 1H, H_{6'}), 2.03 – 2.07 (m, 1H, H_{3'}), 1.60 – 1.64 (m, 2H, H₃, H_{5'}), 1.33 – 1.47 (m, 1H), 1.23 – 1.28 (m, 1H), 0.94 – 1.14 (m, 2H), 0.91 (d, 3H, ³J = 6.4, H₇), 0.80 (d, 3H, ³J = 6.8, H₉), 0.76 – 0.84 (m, 1H, H₃), 0.67 (d, 3H, ³J = 7.2, H₉); ¹³C NMR (62.9 MHz, δ): 166.0 (C=O), 148.7 (C₂), 133.5 (C₄), 131.7 (C₆), 131.1 (C₃), 128.4 (C₅), 124.9 (C₁), 80.4 (C_{1'}), 52.9 (CH₃O), 48.3 (C_{2'}), 42.5 (C_{6'}), 34.4 (C_{4'}), 32.1 (C_{5'}), 25.6 (C_{8'}), 23.6 (C_{3'}), 22.5 (C_{7'}), 21.2 (C_{9'}), 15.9 (C_{9'}).

(-)-Menthyl (S)-2-nitrobenzenesulfinate (**S-2b**; 78% yield (for both diastereomers); R_f 0.47 (pentane/diethyl ether 60:40). Clear yellow solid; [α]_D²⁰ -413.9 (c 1.95, CHCl₃); Lit. (Hajipour and Islami 2000): -447.3 (c 1.5, acetone); ¹H NMR (400 MHz, δ): 8.36 (dd, 1H, ³J = 7.6, ⁴J = 1.2, H₆), 8.23 (dd, 1H, ³J = 8.0, ⁴J = 1.2, H₃), 7.92 (dt, 1H, ³J = 7.6, ⁴J = 1.2, H₄), 7.73 (dt, 1H, ³J = 7.6, ⁴J = 1.6, H₅), 4.16 (dt, 1H, ³J = 10.8, ³J = 4.4, H_{1'}), 2.34 – 2.39 (m, 1H, H_{6'}), 2.03 – 2.06 (m, 1H, H_{3'}), 1.65 – 1.71 (m, 2H, H₂, H₆), 1.45 – 1.55 (m, 2H, H₄), 1.04 – 1.17 (m, 2H, H₅, H₈), 0.98 (d, 3H, ³J = 6.8, H₇), 0.82 (d, 3H, ³J = 7.2, H₉), 0.82 – 0.88 (m, 1H, H₃), 0.76 (d, 3H, ³J = 6.8, H₉); ¹³C NMR (100.6 MHz, δ): 145.7 (C₂), 142.8 (C₁), 134.9 (C₄), 132.4 (C₅), 126.3 (C₆), 125.0 (C₃), 81.1 (C_{1'}), 48.0 (C_{2'}), 41.4 (C_{6'}), 34.0 (C_{4'}), 31.9 (C_{5'}), 25.3 (C_{8'}), 23.3 (C_{3'}), 22.2 (C_{7'}), 20.9 (C_{9'}), 15.6 (C_{9'}); IR (KBr) ν = 1531 (NO₂), 1456, 1349, 1137, 949, 757; EIMS (m/z): 348 (11) [M + Na], 228 (9), 210 (100); HRMS (ESI, m/z): [M + Na]⁺ calcd for C₁₆H₂₃NO₄NaS: 348.1245, found 348.1247.

(-)-Menthyl (R)-2-nitrobenzenesulfinate (**R-2b**; R_f 0.38 (pentane/diethyl ether 60:40). Clear yellow solid [α]_D²⁰ +266.2 (c 1.42 in CHCl₃); ¹H NMR (400 MHz, δ): 8.32 (dd, 1H, ³J = 8.0, ⁴J = 1.6, H₆), 8.23 (dd, 1H, ³J = 8.0, ⁴J = 1.2, H₃), 7.90 (dt, 1H, ³J = 7.6, ⁴J = 1.2, H₄), 7.72 (dt, 1H, ³J = 8.0, ⁴J = 1.6, H₅), 4.26 (dt, 1H, ³J = 10.8, ³J = 4.4, H_{1'}), 2.22 – 2.28 (m, 1H, H_{6'}), 1.78 – 1.85 (m, 1H, H₃), 1.62 – 1.66 (m, 2H, H₂, H₆), 1.41 – 1.51 (m, 1H, H₄), 1.18 – 1.33 (m, 2H, H₅, H₈), 0.99 – 1.10 (m, 1H, H₄), 0.91 (d, 3H, ³J = 6.8, H₇), 0.76 – 0.84 (m, 1H, H₃), 0.78 (d, 3H, ³J = 6.8, H₉), 0.74 (d, 3H, ³J = 6.8, H₉); ¹³C NMR (100.6 MHz, δ): 145.3 (C₂), 142.9 (C₁), 135.0 (C₄), 132.5 (C₅), 126.1 (C₆), 125.0 (C₃), 83.1 (C_{1'}), 48.4 (C_{2'}), 43.4 (C_{6'}), 33.9 (C_{4'}), 31.8 (C_{5'}), 25.0 (C_{8'}), 23.1 (C_{3'}), 22.1 (C_{7'}), 21.0 (C_{9'}), 15.4 (C_{9'}).

(-)-Menthyl 4-nitrobenzenesulfinate **2c** (mixture of diastereomers); 75% yield; R_f 0.2 (pentane/ethyl acetate 90:10). White solid; mp 75 °C; [α]_D²⁰ -100.7 (c 0.4, CHCl₃); for a de 32%, dr 34/66; Lit. (Hajipour and Islami 2000): -438 (c 1.2, acetone); ¹H NMR (400 MHz, δ): 8.39 (t, 2H, ³J = 8.8, H₃), 7.92 (d, 2H, ³J = 8.8, H₂), 4.23 & 4.28 (dt, 1H, ³J = 10.7, ³J = 4.5, H_{1'}), 0.72 – 2.36 (m, 20H); ¹³C NMR (62.9 MHz, δ): 152.4, 150.2, 126.6, 126.1, 124.4, 124.3, 83.7, 81.7, 48.8, 48.0, 43.7, 42.9, 34.0, 33.9, 32.0, 31.9, 25.8, 25.5, 23.3, 23.2, 22.2, 22.0, 21.0, 20.9, 15.8, 15.6; IR (KBr)

ν = 1529, 1346, 1141, 763; EIMS (m/z (%)): 326 (1) [M⁺], 170 (7), 139 (33), 83 (100), 69 (19), 55 (48).

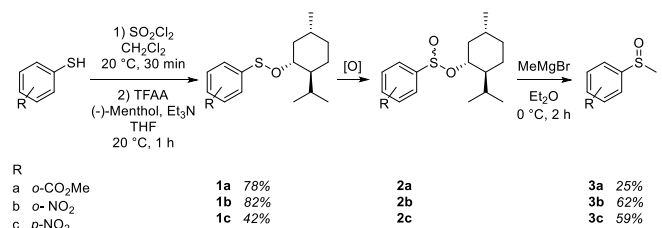
(R)-(+)-Methyl 2-methylsulfinylbenzoate (**R-3a**; Yield 25%; R_f 0.2 (ethyl acetate/pentane 80:20). White solid; [α]_D²⁰ +139.0 (c 1, CHCl₃); Lit. (Pitchen et al. 1984), for 60% ee: +84.0 (c 0.4, acetone); ¹H NMR (400 MHz, δ): 8.32 (dd, 1H, ³J = 7.9, ⁴J = 1.2), 8.09 (dd, 1H, ³J = 7.8, ⁴J = 1.2), 7.84 (dt, 1H, ³J = 8.0, ⁴J = 1.3), 7.58 (dt, 1H, ³J = 7.1, ⁴J = 1.2), 3.96 (s, 3H, CH₃O), 2.85 (s, 3H, CH₃).

(R)-(+)-Methyl 2-nitrophenyl sulfoxide (**R-3b**; Yield 62%; R_f 0.2 (ethyl acetate). White solid; [α]_D²⁰ +164.6 (c 1, CHCl₃); Lit. (Brunel and Kagan 1996), for 75% ee: +118.5. ¹H NMR (400 MHz, δ): 8.03 (d, 1H, ³J = 8.0), 6.92 – 7.01 (m, 2H), 6.62 (t, 1H, ³J = 7.1), 2.22 (s, 3H, CH₃).

Methyl 4-nitrophenyl sulfoxide **3c**; Yield 59%; R_f 0.2 (ethyl acetate). White solid; [α]_D²⁰ +50.0 (c 1 in CHCl₃); Lit. (Brunel et al. 1995), for 99.3% ee: +156.9 (c 0.75 in CHCl₃); ¹H NMR (400 MHz, δ): 8.36 (d, 2H, ³J = 8.2), 7.80 (d, 2H, ³J = 7.9), 2.28 (s, 3H, CH₃).

Results and Discussion

In order to demonstrate its potential, the sequence we described earlier Hamel et al. 2005) has been extended to other substrates. Thus, aryl methyl sulfoxides where the aromatic ring is functionalized with either a nitro (in *ortho* or *para* position) or an *ortho*-methoxycarbonyl groups were prepared following this strategy. The overall reaction sequence is described in Scheme 1. Some of the diastereomerically pure sulfinate esters **2a**, **b** and **c** have previously been reported by other groups. **2a** was prepared starting from the corresponding sulfinyl chloride which reacts with menthol, with a low diastereoselectivity (Klunder and Sharpless 1987). Compounds **2b** and **2c** were obtained from the reaction of *ortho*- or *para*-nitrophenyldisulfide with menthol in the presence of lead tetraacetate, with a moderate diastereomeric excess (Hajipour and Islami 2000). Another method consists in reacting the sulfonyl chloride and the alcohol in the presence of trimethylphosphite in dichloromethane (Lee et al. 1994) or under solid state conditions (Hajipour and Islami 1999). Crystal structure of (**S-2a**) has even been assigned, with a hydrogen bond linking the oxygen of the sulfinate ester with the hydrogen located in the *para* position of the methoxycarbonyl group (Altamura et al. 2013).



Scheme 1. Synthesis of sulfoxides **3a-c** from the corresponding arylthiols.

In the literature the three sulfoxides **3a-c** have been prepared in an (almost) enantiopure form. Some generic methods for their preparation involve either the enantioselective oxidation of the corresponding sulfide, catalyzed for instance with an organometallic chiral complex, with an enzyme, or via the synthesis of chiral sulfinate esters.

Table 1 gives some examples of the oxidation of the prochiral sulfide leading to the sulfoxides **3a-c**. These examples were sorted so that both enantiomeric excess and chemical yield were optimum.

According to the description of the synthesis given in Scheme 1, we started from commercial aromatic thiols. Methyl thiosalicylate was prepared according to a published reaction (Sasaki et al. 1991). The thiols were first converted into sulfonyl chlorides, then reacted with (–)-menthol in the presence of triethylamine and a catalytic amount of trifluoroacetic acid anhydride (TFAA). Enantiopure menthyl sulfenyl ester were thus obtained in good yields, from 50 up to 78%.

The second step consists in the diastereoselective oxidation to afford the menthyl sulfinates. Various methods can be used for

the oxidation of sulfenyl esters to their corresponding sulfinates. We used both achiral and chiral oxidants, the two chiral compounds being the (+)- and the (–)-isomers of (8,8-dichlorocamphorylsulfonyl)oxaziridine (hereafter, designated as (+)-Ox and (–)-Ox, for the sake of clarity), whereas simple oxidants were either *m*CPBA or the couple NBS/H₂O. Oxidations of **1b** and **1c** were performed only with achiral oxidants. Diastereoselectivity was measured following the ¹H NMR chemical shift from the CH-O of the menthyl moiety. The results are summarized in Table 2.

Table 1. Some examples of selective sulfide oxidation leading to enantiopure sulfoxides 3a-c.

Sulfoxide	Config.	Yield (%)	ee (%)	Method	Ref.
3a	(<i>R</i>)	53	99	Ti(<i>O</i> - <i>i</i> -Pr) ₄ /(<i>R,R</i>)-DET 1:4	De Sio et al. 2010
3a	(<i>R</i>)	95	80	Mn(OTf) ₂ /porphyrin deriv./H ₂ O ₂	Dai et al. 2014
3a	(<i>S</i>)	n.d.	82	Myoglobin active site mutants L29H/H64L	Ozaki et al. 1999
3b	(<i>R</i>)	90	92	H ₂ O ₂ , chiral amino alcohol, VO(acac) ₂	Aydin 2013
3b	(<i>S</i>)	84	99	H ₂ O ₂ , Al salalen	Matsumoto et al. 2008
3c	(<i>R</i>)	95	99.5	H ₂ O ₂ , MgSO ₄ , chiral Brønsted acid	Liao et al. 2012
3c	(<i>S</i>)	92	92	H ₂ O ₂ , Ti Salen	Saito et al. 2001
3c	(<i>S</i>)	66	96	<i>N,N'</i> -dioxide-iron(III) complex	Wang et al. 2020

Table 2. Diastereoselective oxidation of arenesulfenyl ester 1

Entry	Sulfenyl	Oxidant	Conditions	Sulfinate	Yield (%)	dr	de (%)
1	1a	NBS/H ₂ O	CH ₃ CN/H ₂ O, 20 °C, 2 h	2a	68	69:31	38
2	1a	<i>m</i> CPBA	CH ₂ Cl ₂ , -78 → 20 °C	2a	90	45:55	10
3	1a	(+)-Ox	CCl ₄ , 20 °C, 15 d	2a	56	39:61	22
4	1a	(–)-Ox	CCl ₄ , 20 °C, 15 d	2a	63	65:35	30
5	1b	NBS/H ₂ O	CH ₃ CN/H ₂ O, 20 °C, 2 h	2b	6	72:28	44
6	1b	<i>m</i> CPBA	CH ₂ Cl ₂ , -78 → 20 °C	2b	78	42:58	16
7	1c	NBS/H ₂ O	CH ₃ CN/H ₂ O, 20 °C, 2 h	2c	69	74:26	48
8	1c	<i>m</i> CPBA	CH ₂ Cl ₂ , -78 → 20 °C	2c	75	34:66	32

Table 3. Transformation of arenesulfinate esters 2 into enantioenriched sulfoxides 3

Entry	Sulfinate	dr (config.) ^a	Sulfoxide	Yield (%)	ee (%) (config.) ^a	Measured [α] _D ²⁰
1	2a	100:0 ^b (<i>S</i>)	3a	25	100 (<i>R</i>)	+84.0 (c 1, CHCl ₃)
2	2b	100:0 ^b (<i>S</i>)	3b	62	100 (<i>R</i>)	+164.6 (c 1, CHCl ₃)
3	2c	34:66 (<i>S</i>)	3c	59	32 (<i>R</i>)	+50.0 (c 1, CHCl ₃)

^a absolute configuration at sulfur atom

^b dr after separation of diastereomers

All these oxidations performed smoothly and led to good conversions, but took an unexpected long time when performed with the oxaziridine (up to 15 days). As previously stated, oxidation with NBS/H₂O couple did not favor the same diastereomer as when performing the oxidation with *m*CPBA (Hamel et al. 2005). For the three sulfinate esters **2**, the observed diastereomeric excess was in the range of 10-48%, so slightly lower than those obtained with *ortho*-phosphorylated menthyl benzenesulfinate (Hamel et al. 2005). Moreover, the best diastereomeric ratio values were obtained when oxidizing compounds **1** with the NBS/H₂O couple. Surprisingly, the best de was observed with **1c**, suggesting that the position of the substituent had almost no influence on the steric hindrance, the latter being therefore driven by the menthyl moiety. Therefore, one or the other diastereomer can be favored either by using *m*CPBA or NBS/H₂O or by using (–)- or (+)-menthol.

Starting from the diastereomeric mixtures obtained respectively in entries 2 and 6 from Table 2, the diastereomerically pure major sulfinates **2a** and **2b** have been successfully separated using silica gel chromatography or by separative crystallization in acetone. In the case of **2c** (entry 8, Table 2), the diastereomer separation was not possible. Specific rotation for optically pure compounds **2a** and **2b** are negative with respective values of –360.0 and –453.2 (c 0.6 and 1 in chloroform). These are slightly more negative than reported in the literature with respective [α]_D²⁰ of –348.6 and –447.7 (c 1.18 (Klunder and Sharpless 1987) and 1.5 in acetone (Hajipour and Islami 2000)). According to the literature, these sulfinate esters have the (*S*) configuration at the sulfur atom.

From the two optically pure sulfinate esters (*S*)-**2a** and (*S*)-**2b** and the optically enriched compound **2c**, the preparation of the

corresponding methyl aryl sulfoxides **3a-c** has been performed. As methylmagnesium bromide is able to attack both the electrophilic sulfur atom and the ester function of a sulfinate, to limit the second undesired process, the reaction was performed at 0 °C with a very slight excess of Grignard reagent. However, a low yield was obtained for **3a** (25%), whereas **3b** and **3c** were isolated with satisfactory yields of 62% and 59%, respectively (Table 3). The comparison of the specific rotation values of the obtained aryl methyl sulfoxides with data from the literature (see in the experimental part), allowed us to assign the absolute (*R*) configuration at sulfur in the three cases. This was expected to be obtained after full inversion of configuration at the sulfur atom from the starting corresponding (*S*)-sulfinates **2a-c** leading to sulfoxides (*R*)-**3a** and (*R*)-**3b** in an optically pure form (entries 1 and 2, Table 3), and (*R*)-**3c** with 32% ee (entry 3, Table 3). Despite the fact that this method was exemplified on a small number of substrates, the obtained results are encouraging for application on other arylsulfides bearing an electron withdrawing substituent on the aromatic ring. The oxidation of sulfenyl esters was performed with simple oxidants such as *m*CPBA or NBS/H₂O and the asymmetric induction was provided by the cheap enantiopure menthol. Since the chiral induction is provided by the alcohol, one can expect that this strategy should work not only for arylsulfenates but also for alkylsulfenates as well.

Conclusion

In conclusion, an efficient method for the access to three *ortho* and *para* substituted aryl methyl sulfoxides is described herein.

The diastereoselective oxidation of sulfenate to sulfinate ester is the key step, leading to diastereomeric excesses ranging from 10 to 48%. After separation of the diastereomers and reaction with methyl Grignard, two enantiopure sulfoxides, the (*Rs*)-(2-methoxycarbonylphenyl) **methyl sulfoxide** and the (*Rs*)-2-nitrophenyl **methyl sulfoxide**, and one enantioenriched (32% ee) were obtained.

Acknowledgements

The Authors gratefully acknowledge financial support from the Ministère de la Recherche for the grant allowed to MH for his PhD thesis. **The Reviewers and the Editor are also gratefully acknowledged for their valuable comments.**

Conflict of interest statement

The Authors declare no conflict of interest.

REFERENCES

- Abrunhosa I, Drabowicz J, Grach G, Gulea M, Hamel M, Masson S, Mikolajczyk M, Vazeux M (2005) New chiral *ortho*-*P,S*-difunctionalized aromatic compounds. Phosphorus, Sulfur and Silicon 180(5-6):1267-1272. <https://doi.org/10.1080/10426500590911467>
- Altamura M, Guidi A, Jierry L, Paoli P, Rossi P (2013) (1*R*,2*S*,5*R*)-(-)-Menthyl (S)-2-(methoxycarbonyl)benzenesulfinate. Acta Cryst E69:o731. <https://doi.org/10.1107/S1600536813009112>
- Aydin AE (2013) Synthesis of novel β -amino alcohols and their application in the catalytic asymmetric sulfoxidation of sulfides. Tetrahedron: Asymmetry 24(8):444-448. <https://doi.org/10.1016/j.tetasy.2013.03.011>
- Bentley R (2005) Role of sulfur chirality in the chemical processes of biology. Chem Soc Rev 34(7):609-624. <https://doi.org/10.1039/B418284G>
- Brunel J-M, Diter P, Duetsch M, Kagan HB (1995) Highly Enantioselective Oxidation of Sulfides Mediated by a Chiral Titanium Complex. J Org Chem 60(24):8086-8088. <https://doi.org/10.1021/jo00129a060>
- Brunel J-M, Kagan HB (1996) Catalytic enantioselective oxidation of sulfides with a chiral titanium complex. Bull Soc Chim Fr 133(11): 1109-1115.
- Cotton H, Elebring T, Larsson M, Li L, Sørensen H, von Unge S (2000) Asymmetric synthesis of esomeprazole. Tetrahedron: Asymmetry 11(18):3819-3825. [https://doi.org/10.1016/S0957-4166\(00\)00352-9](https://doi.org/10.1016/S0957-4166(00)00352-9)
- Dai W, Li G, Wang L, Chen B, Shang S, Lv Y, Gao S (2014) Enantioselective oxidation of sulfides with H₂O₂ catalyzed by a pre-formed manganese complex. RSC Adv 4(87):46545-46554. <https://doi.org/10.1039/C4RA09832C>
- De Sio V, Massa A, Scettri A (2010) Chiral sulfoxides as activators of allyl trichlorosilanes in the stereoselective allylation of aldehydes. Org Biomol Chem 8(13):3055-3059. <https://doi.org/10.1039/C002988B>
- Fernández A, Khiar N (2003) Recent Developments in the Synthesis and Utilization of Chiral Sulfoxides. Chem Rev 103(9):3651-3706. <https://doi.org/10.1021/cr990372u>
- Hajipour A, Islami F (1999) A convenient and highly diastereoselective synthesis of optically active sulfinate esters from sulfonyl chlorides under solid state conditions. Indian J Chem 38B(04):461-462. <http://nopr.niscair.res.in/handle/123456789/16422>
- Hajipour AR, Islami F (2000) Highly diastereoselective synthesis and easy method for synthesis of optically active sulfinate esters from aromatic disulfides. Indian J Chem 39B(07):536-538. <http://nopr.niscair.res.in/handle/123456789/22538>
- Hamel M, Grach G, Abrunhosa I, Gulea M, Masson S, Vazeux M, Drabowicz J, Mikolajczyk M (2005) Asymmetric oxidation of sulfenates to sulfates as a new route to optically active *ortho*-phosphorylated phenyl sulfoxides. Tetrahedron: Asymmetry 16(20):3406-3415. <https://doi.org/10.1016/j.tetasy.2005.09.005>
- Hamel M, Lecinq M, Gulea M, Kozelka J (2013) *Ortho*-(methylsulfonyl)phenylphosphonates and derivatives: Synthesis and applications as mono- or bidentate ligands for the preparation of platinum complexes. J Organomet Chem 745-746:206-213. <https://doi.org/10.1016/j.jorganchem.2013.07.069>
- Han J, Soloshonok VA, Klika KD, Drabowicz J, Wzorek A (2018) Chiral sulfoxides: advances in asymmetric synthesis and problems with the accurate determination of the stereochemical outcome. Chem Soc Rev 47(4):1307-1350. <https://doi.org/10.1039/C6CS00703A>
- Kielbasiński P, Łuczak J, Cierpień T, Błaszczak J, Sieroń L, Wiktorska K, Lubelska K, Milczarek M, Chilmończyk Z (2014) New enantiomeric fluorine-containing derivatives of sulfuraphane: Synthesis, absolute configurations and biological activity. Eur J Med Chem 76:332-342. <https://doi.org/10.1016/j.ejmech.2014.02.036>
- Klunder JM, Sharpless KB (1987) Convenient synthesis of sulfinate esters from sulfonyl chlorides. J Org Chem 52(12):2598-2602. <https://doi.org/10.1021/jo00388a051>
- Laforgia M, Cerasino L, Margiotta N, Capozzi MAM, Cardellicchio C, Naso F, Natile G (2004) Synthesis and Characterization of Platinum(II) Complexes of Diethyl [(Methylsulfonyl)methyl]phosphonate: Potential Drugs against Bone Tumors. Eur J Inorg Chem (17):3445-3452. <https://doi.org/10.1002/ejic.200400195>
- Laforgia M, Margiotta N, Capitelli F, Bertolasi V, Natile G (2005) Platinum Complexes with the Novel Ligand Diethyl [(Methylsulfonyl)-methyl]phosphonate (SMP): Solid-State Characterization of Potassium Trichloro(SMP)platinum(II) which, in Solution, Gives Dichloro(SMP)-platinum(II) and Potassium Chloride. Eur J Inorg Chem (9):1710-1715. <https://doi.org/10.1002/ejic.200400842>
- Lee AWM, Chan WH, Tao Y, Lee YK (1994) Chiral acetylenic sulfoxide in enantioselective synthesis of tetrahydroisoquinoline and tetrahydro- β -carboline alkaloids. Total synthesis of (*R*)-(+)-Carnegine and (*R*)-(+)-tetrahydroharman. J Chem Soc Perkin Trans 4:477-481. <https://doi.org/10.1039/P19940000477>
- Liao S, Čorić I, Wang Q, List B (2012) Activation of H₂O₂ by Chiral Confined Brønsted Acids: A Highly Enantioselective Catalytic Sulfoxidation. J Am Chem Soc 134(26):10765-10768. <https://doi.org/10.1021/ja3035637>
- Matsumoto K, Yamaguchi T, Fujisaki J, Saito B, Katsuki T (2008) Aluminum Oxidation Catalysis under Aqueous Conditions: Highly Enantioselective Sulfur Oxidation Catalyzed by Al(salalen) Complexes. Chem – Asian J 3(2):351-358. <https://doi.org/10.1002/asia.200700328>
- Mauger C, Vazeux M, Albinati A, Kozelka J (2000) Reaction between the diaqua form of cisplatin and 2-methylsulfonylphenylphosphonic acid yields a dinuclear phosphonato-bridged complex via NH₃ elimination. Inorg Chem Commun 3(12):704-707. [https://doi.org/10.1016/S1387-7003\(00\)00170-2](https://doi.org/10.1016/S1387-7003(00)00170-2)
- O'Mahony GE, Kelly P, Lawrence SE, Maguire AR (2011) Synthesis of enantioenriched sulfoxides. ARKIVOC i:1-110. <https://doi.org/10.3998/ark.5550190.0012.101>
- Otocka S, Kwiatkowska M, Madalińska L, Kielbasiński P (2017) Chiral Organosulfur Ligands/Catalysts with a Stereogenic Sulfur Atom: Applications in Asymmetric Synthesis. Chem Rev 117(5):4147-4181. <https://doi.org/10.1021/acs.chemrev.6b00517>
- Ozaki S-I, Yang H-J, Matsui T, Goto Y, Watanabe Y (1999) Asymmetric oxidation catalyzed by myoglobin mutants.

- Tetrahedron: Asymmetry 10(1):183-192.
[https://doi.org/10.1016/S0957-4166\(98\)00498-4](https://doi.org/10.1016/S0957-4166(98)00498-4)
- Pellissier H (2006) Use of chiral sulfoxides in asymmetric synthesis. Tetrahedron 62(24):5559-5601.
<https://doi.org/10.1016/j.tet.2006.03.093>
- Pitchen P, Dunach E, Deshmukh MN, Kagan HB (1984) An efficient asymmetric oxidation of sulfides to sulfoxides. J Am Chem Soc 106(26):8188-8193.
<https://doi.org/10.1021/ja00338a030>
- Saito B, Katsuki T (2001) Ti(salen)-catalyzed enantioselective sulfoxidation using hydrogen peroxide as a terminal oxidant. Tetrahedron Lett 42(23):3873-3876.
[https://doi.org/10.1016/S0040-4039\(01\)00590-1](https://doi.org/10.1016/S0040-4039(01)00590-1)
- Sasaki K, Tashima Y, Nakayama T, Hirota T (1991) Polycyclic *N*-hetero compounds. XXXVIII. Synthesis and evaluation of antidepressive activity of [1]benzothieno[2',3':4,5]furo[3,2-d]pyrimidines and their precursors J Heterocycl Chem 28(2):269-272. <https://doi.org/10.1002/jhet.5570280211>
- Wang F, Feng L, Dong S, Liu X, Feng X (2020) Chiral *N,N'*-dioxide-iron(III)-catalyzed asymmetric sulfoxidation with hydrogen peroxide. Chem Commun 56(21):3233-3236.
<https://doi.org/10.1039/D0CC00434K>
- Wojaczyńska E, Wojaczyński J (2010) Enantioselective Synthesis of Sulfoxides: 2000–2009. Chem Rev 110(7):4303-4356.
<https://doi.org/10.1021/cr900147h>
- Wojaczyńska E, Wojaczyński J (2020) Modern Stereoselective Synthesis of Chiral Sulfinyl Compounds. Chem rev 120(10):4578-4611. <https://doi.org/10.1021/acs.chemrev.0c00002>