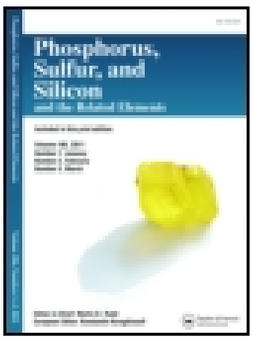

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Asymmetric synthesis of (*S,R*)- and (*R,R*)-methiin stereoisomers

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ABSTRACT

An asymmetric synthesis of (+)- and (–)-methiine (*S*-methyl-(*R*)-cysteine sulfoxide) diastereomers has been developed. These natural sulfur compounds were isolated from a variety of *Brassica* vegetables. As the starting compound, (*R*)-cysteine was used, which was methylated to form (*R*)-*S*-methylcysteine. Then the oxidation of *S*-methylcysteine with *tert*-butyl hydroperoxide catalyzed by the chiral tetra(isopropylate)titanium/(*S*)- or (*R*)-Binol complex led to the formation of (1 *R*,2*S*)-(+)- or (1 *R*,2*R*)-(–)-methiin stereomers.

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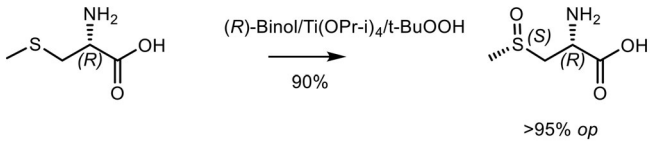
KEYWORDS
Methiine; chiral sulfoxides; cysteine; asymmetric oxidation

GRAPHICAL ABSTRACT



Introduction

S-Alk(en)yl-cysteine sulfoxides are non-protein sulfur-containing aminoacids found in representatives of the *Alliaceae* family and are the precursors of tear and flavoring substances found in the agronomically important *Allium* family. Traditionally, *Allium* species, especially onions (*Allium cepa L*) and garlic (*A. sativum*), have been used for centuries in European, Asian and American folk medicines to treat various pathologies [1–4]. Examples of chiral sulfoxides include natural (+)-*S*-methyl-L-cysteine sulfoxide (Methiin), (+)-*S*-allyl-cysteine sulfoxide (Alliin), as well as a number of other amino acid sulfoxides present in some plants, determine their unique properties (Scheme 1).

Chiral sulfoxides, including *S*-methylcysteine sulfoxide, are found among some aminoacids in mammalian metabolites, while L-cysteine sulfoxides have been found in *Brassica* plants and a number of other natural sources, some of which are food products [4, 5]. For example, the natural *S*-methyl-(*R*)-cysteine sulfoxide was isolated from plants such as *Brassica oleracea* cabbage, cauliflower, mustard, broccoli, turnip, etc., which have a number of useful properties [1–3]. *S*-methyl-(*R*)-cysteine-(*S*)-sulfoxide is present in garlic [5], onions [6], nuts [7], carrots [8], apples [9, 10], and bananas [11]. The unique healing properties of garlic are largely determined by the presence of aminoacid sulfoxides [1]. Cysteine sulfoxide determines the characteristic smell and taste of garlic and onions [12, 13]. *S*-methyl-(*R*)-cysteine sulfoxide was found in the non-protein fraction of turnip roots (*Brassica rapa*) and a number of other plants [2]. In addition, *S*-methyl-L-cysteine-(*S*)-sulfoxide [(+)-Methiin] and *S*-allyl-L-cysteine (*S*)-sulfoxide [(+)-Alliin] are promising food additives and medicinal drugs possessing antibiotic [14, 15], cardiovascular and antioxidant [16, 17] properties. These compounds exhibit anti-inflammatory [9], antidiabetic [18, 19], anti-Alzheimer's [20] and anticholesterolemic [21] properties. Of particular interest is the antidiabetic efficacy of (+)-Methiin [19]. It was found that the optical stereoisomers (+)- and (–)-Methiin, as well as other chiral sulfoxides, significantly differ in their biological activity. For example, in the case of esomeprazole, the activity of one sulfoxide enantiomer significantly exceeds the activity of its antipode. Therefore, it is important to develop methods for the synthesis of methiine stereoisomers and its analogs

Results and discussion

Chiral aminoacid sulfoxides are usually prepared by enzymatic oxidation of *S*-substituted aminoacids, for example cysteine. Asymmetric oxidation of sulfur-containing L-aminoacids was achieved using Fe(II)/α-ketoglutarate-dioxygenase previously found in *Bacillus thuringiensis* strain 2e2. This enzyme catalyzed the sulfoxidation of *S*-methyl-L-cysteine, *S*-ethyl-L-cysteine, and *S*-allyl-L-cysteine into the corresponding (*S*)-configured sulfoxides such as (+)-methiin and (+)-alliin, which are responsible for valuable physiological activities in mammals, and have high stereoselectivity (Scheme 2) [22].

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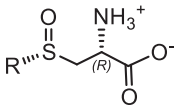
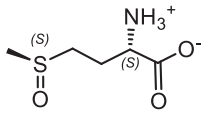
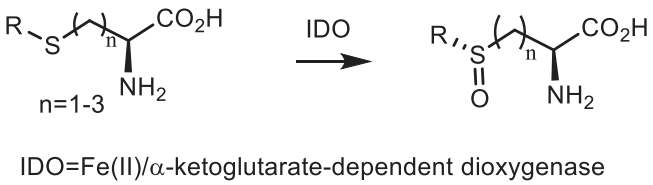


R = Me (Methiin), CH_2=$CHCH_2$ (Alliin), Pr (Propiin), CH_3CH=CH (Isoalliin), Et (Ethiin), Bu (Butiin)



Methionine sulfoxide

Scheme 1. Some natural sulfur-containing aminoacids.



IDO=Fe(II)/α-ketoglutarate-dependent dioxygenase

Scheme 2. Oxidation of *S*-substituted aminoacids by Fe(II)/α-ketoglutarate-dioxygenase.

To obtain cysteine-sulfoxide stereoisomers, asymmetric oxidation of sulfides to sulfoxides using Isoleucine dioxygenase and Chloroperoxidase in combination with hydrogen peroxide was used [20]. Using this method, methionine sulfoxide, derivatives of (+) - *S*-methyl-(*R*)-cysteine sulfoxide (**3**) and (+)-*S*-allyl-cysteine sulfoxide were also obtained (Scheme 3).

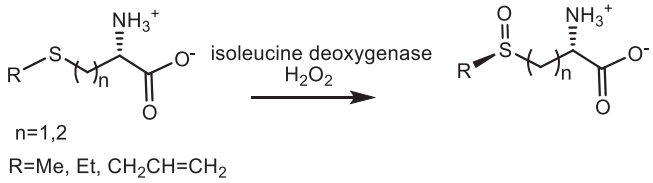
Treatment of *N*-methoxycarbonyl derivatives of *S*-methyl-L-cysteine with a chloroperoxidase (CPO)/hydrogen peroxide resulted in the oxidation at sulfur to produce the (*RS*) sulfoxide in good diastereomeric excess. Some other sulfur-containing amino acids were also obtained by this method (Scheme 4).

(*R,S*)-Methionine sulfoxide was obtained with a moderate diastereomeric excess by kinetically controlled hydrolysis of the aminoacid ester catalyzed by the enzymes: α-Chymotrypsin, *Aspergillus,* sp. Protease, Subtilisin Carlsberg, *Aspergillus* lipase (Scheme 5). [20]. It has been reported that stereoselective biocatalytic oxidation of sulfides to sulfoxides can be carried out using *Penicillium citreoviride*, although no stereochemical details of this method have been reported [15–17].

The oxidation of methionine and cysteine derivatives to sulfoxides with chlorine dioxide has also been reported [23]. Oxidation of sulfides with aqueous ClO_2 at 30–40 °C led to the formation of corresponding sulfoxides in high yield 95–97%, but with low stereoselectivity.

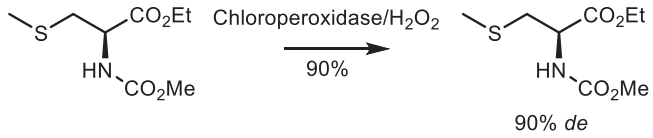
Thus, analyzing the literature data, we drew the conclusion that the existing methods are in most cases rather experimentally complicated since hard-to-reach enzymes are required and do not always give products with high *de* and *ee*. Therefore, the development of a simple stereoselective method for the synthesis of optically active cysteine sulfoxides is undoubtedly interesting.

The main strategy, which we have proposed for the methiin synthesis, was at first to methylate the aminoacid and then to oxidize asymmetrically the sulfide group (Scheme 6). In this work, for this purpose, we used natural cysteine, the thio group of which was methylated to form *S*-methylcysteine, as the initial reagent. Then, the *S*-methylcysteine was oxidized to form diastereomers (1 *R*, 2*S*)- and (1 *R*, 2 *R*)-*S*-methylcysteine sulfoxide.



R=Me, Et, CH_2CH=CH_2

Scheme 3. Sulfoxidation of methionine using isoleucine dioxygenase/hydrogen peroxide.

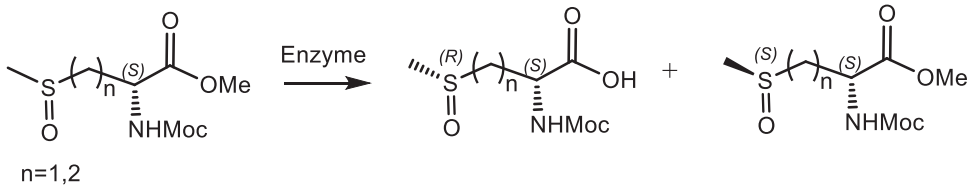


Scheme 4. Biocatalytic oxidation of *N*-Moc-methylcysteinate with chloroperoxidase (CPO)/hydrogen peroxide.

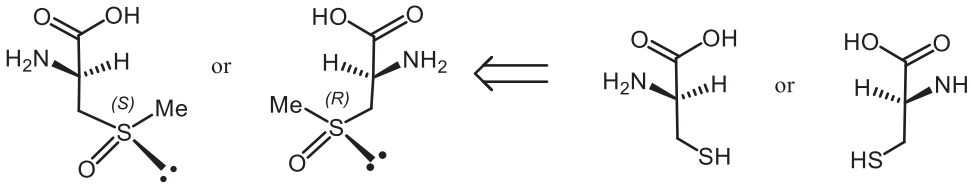
Oxidation of (*R*)-**1** with hydrogen peroxide led to the formation of racemic *S*-methyl-(*R*)-cysteine sulfoxide **2** with a yield of ∼100% without transferring chirality from the chiral C*-NH_2 group to the sulfur atom of the MeS group (Scheme 7). The reaction proceeds similarly in other known cases of the *S*-methylcysteine oxidation by achiral oxidizing agents, in particular, as was shown in the case of publication [23].

Therefore, we concluded that, in order to achieve the highest enantioselectivity of oxidation and to obtain optically pure methylcysteine sulfoxide, it is necessary to use an asymmetric oxidation reagent effective for this case. To this end, we investigated several known asymmetric oxidizing agents, in particular the Sharpless asymmetric oxidation reagent [24], but without much success. After several attempts, we drew the conclusion that *tert*-butyl hydroperoxide catalyzed by a chiral complex of titanium tetra(isopropylate) with the optically active (*S*)- or (*R*)-binol is the best reagent for the asymmetric oxidation of *S*-methylcysteine. Oxidation with the complex containing (*R*)-binol led to the (1 *R*, 2*S*)-stereoisomer **3** in yield 90% and with optical purity higher than 80%, which, after purification with crystallization or column chromatography, was obtained with a purity of 95% *op* (optical purity). Similarly, the oxidation of methylcysteine (*R*)-**1** with a complex containing (*S*)-binol led to the formation of the (1 *R*, 2 *R*)-stereoisomer **4** in yield of 80% and with 80% *de*, which was obtained after chromatography with an optical purity of 95% (Scheme 8).

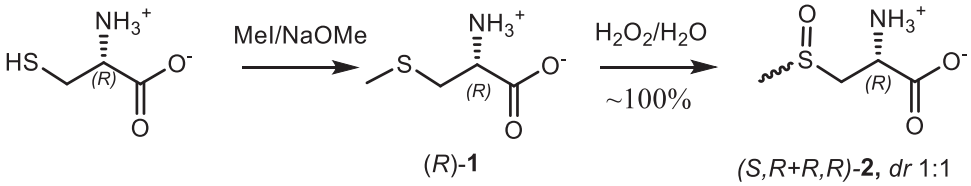
The structure of the products was confirmed by NMR and chromatography-mass spectrometry. Chemical shifts corresponding to diastereotopic methylene protons (multiplets at 3.2 and 3.60 ppm), methiine CHN group at 4.4 ppm as well as NH_3^+ groups of 4.67–4.78, were observed in the NMR spectrum. Protons of the $CH_3S(O)$-group resonated as a singlet at 2.75 ppm, which indicates the formation of enantiomerically pure methylcysteine sulfoxides **3** or **4** in the form of two diastereomers, since the chirality on the α-C atom was retained, and a new chiral center was formed at the S atom. According to NMR spectroscopy, the ratio of diastereomers before the purification step was 9:1. In the ^{13}C NMR spectrum, signals of all five carbon atoms were



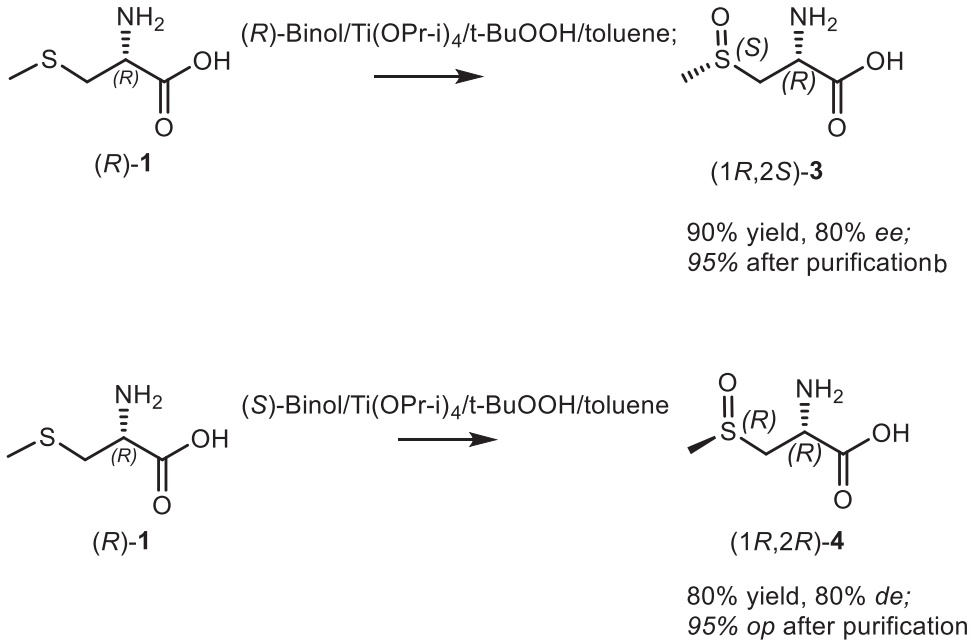
Scheme 5. Kinetically controlled hydrolysis of sulfoaminoacid esters.



Scheme 6. Retro synthesis of (+)- and (–)-methiin.



Scheme 7. Oxidation of *S*-methylcysteine (*R*)-**1** with hydrogen peroxide.



Scheme 8. Asymmetric oxidation of *S*-methylcysteine (*R*)-**1.**

detected. In particular, the carbon of the carboxyl group is present at 169 ppm. Purification of the product by silica gel column chromatography, eluent acetonitrile-water in a ratio of 2:1, allowed us to obtain optically pure *S*-methylcysteine sulfoxide stereoisomers with 95% *de*. The high purity of the synthesized *S*-methylcysteine sulfoxide was confirmed by chromatography–mass spectrometry, which showed the presence of a single signal in the HPLC as well as the presence of the expected mass peak ion.

Thus, we have developed a method to easily obtain the enantiomerically pure chiral cysteine sulfoxides on a preparative laboratory scale using *tert*-butyl hydroperoxide and the chiral catalyst – (*S*)- or (*R*)-binol/titanium tetraisopropylate.

Experimental part

^{1}H NMR and ^{13}C NMR spectra were recorded in a $CDCl_3$ or D_2O solvent on a 500 MHz spectrometer at ambient

temperature. Chemical shifts δ (ppm) are related to TMS ($\delta = 0.00$ ppm) as internal standard. Signal multiplicities are designated as s, singlet; d, doublet; dd, doublet–doublet; t, triplet; m, multiplet; bs, broad singlet. The coupling constants J are given in Hertz. Reagents and solvents were used without special purification, unless otherwise indicated. Column chromatography was performed on silica gel 60 (70–230 mesh) using the indicated eluents. Optical rotations were measured on a 241 Perkin-Elmer polarimeter (D sodium line at 20 °C). Melting points were not corrected. The reactions were carried out in glassware dried over a fire or dried in a dry box. The progress of reactions was monitored by analytical thin layer chromatography (TLC) on glass plates of silica gel 60 F254 (Merck, Darmstadt, Germany) and the products were visualized with anisaldehyde or UV. The purity of all compounds was checked by thin layer chromatography and NMR measurements. HPLC analysis was performed on Chiralpak OD-3 column (hexane: IPA: MeOH = 95:2.5:2.5), flow rate = 0.6 mL/min, $\lambda = 210$ nm).

S-Methyl-L-cysteine (*R*)-1

L-Cysteine (2.42 g, 0.02 mol) was suspended in absolute ethanol (60 mL) and sodium metal (1.84 g, 0.08 mol) was added with cooling. It was stirred for 30 min, and then of methyl iodide (1.4 mL, 0.022 mol) was added. The temperature was raised to room temperature and the reaction mixture was stirred for 30 min. Then water was added until the precipitate was dissolved and the solution was acidified to pH 5. Diethyl ether was added to the mixture, and left in the refrigerator overnight. Precipitated *S*-methylcysteine was filtered off, washed with ether on a filter. Yield 2.4 g, 90%. Mp. 245-250 °C (Ref. [2] mp. 245 °C); $[\alpha]_D^{20} = -34.3$ (c = 1, H_2O), Ref. [2] $[\alpha]_D^{20} = -30.0$ (c = 1.5, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 1.58 (s, 3H, CH_3); 2.46 (m, 1H, CH_2); 2.51 (m, 1H, CH_2); 3.38 (m, 1H, CH); 3.86 (bs, 2H, NH_2). ^{13}C NMR (125.6 MHz, D_2O) δ 14.9, 34.8, 53.5, 173.5.

Oxidation of *S*-methyl-L-cysteine with hydrogen peroxide to (*S* + *R*)/(*R* + *R*)-2

S-Methyl-L-cysteine **1** (2.7 g) was dissolved in water (6 mL), and 30% hydrogen peroxide solution (3 mL) was added dropwise with stirring and the reaction mixture was stirred at 25 °C for 12 h. Then the reaction mixture was evaporated and the residue was recrystallized from aqueous ethanol. The HPLC and NMR showed that the colorless crystalline product is a mixture of (*S*,*R*)- and (*R*,*R*)-diastereomers in a 1:1 ratio. Yield 87%; mp 166 °C (Ref. [25] 167–168 °C). ^{1}H NMR (500 MHz, D_2O) δ 1.74 (s) + 1.75 (s) (3H, CH_3), 3.19 (m) + 3.33 (m) + 3.40 (m) (2H, CCH_2), 4.13 (m) + 4.18 (m) (1H, CH), 4.66 bs (3H, NH_3). MS *m/z* 152 $[(M + 1)]^+$, $C_4H_{10}NO_3S$.

(*R*,*S*)-*S*-Methyl-cysteine sulfoxide [(+)-methiin] 3

Titanium tetraisopropylate (0.5 ml, 0.00178 mol) and water (0.65 mL, 0.035 mol) were added dropwise to a solution of (*R*)-binaphthol (1 g, 0.0035 mol) in dry toluene (30 mL) at room temperature. The reaction mixture was stirred for 1 h, then methylcysteine (2.4 g, 0.0178 mol) was added. It was cooled to –50 °C and *tert*-butyl hydroperoxide (4.9 mL (0.035 mol, 70% aqueous solution) in 10 ml of toluene was added dropwise. The reaction mixture was stirred overnight at room temperature. Then the mixture was evaporated, the residue was dissolved in water and filtered. The solvent was evaporated in vacuo, the residue was dissolved in methylene chloride and refluxed until the formation of a precipitate. The precipitate was filtered off, washed on the filter with methylene chloride. It was then purified by column chromatography, eluent acetonitrile–water 2:1 to yield solid **3** with 95% *ee*. Yield 2.2 g. Mp. 160–165 °C (dec). Ref. [24]: m.p. 160–165 °C (dec.) Ref.: [22], mp. 171–173 °C (decomp). Ref. [25]: mp. 167–168 °C (dec.). $[\alpha]_D^{20} + 118°$ (c = 1.0, H_2O). Ref. [23] $[\alpha]^{20}{}_D = +125.8$ (c = 2.0, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 2.72 (s, 3H), 3.14 (dd, J = 13.87, 7.73 Hz, 1H), 3.37 (dd, J = 13.93, 5.98 Hz, 1H), 4.18 (dd, J = 7.70, 6.05 Hz, 1H). 4.64 bs (NH_3^++H_2O). ^{13}C NMR (125 MHz, D_2O) δ 33.43, 52.01, 63.93, 168.96. ESI-MS, *m/z* = 152 $[M + H]^+$.

(*R*,*R*)-*S*-Methylcysteine sulfoxide [(−)-methiin] 4

(*S*)-Binaphthol (1 g, 0.0035 mol) was dissolved in 30 ml of absolute toluene. Then, 0.5 ml of titanium tetraisopropylate (0.00178 mol) and 0.65 ml of water (0.035 mol) were added dropwise at room temperature. The mixture was stirred for 1 h, then 2.4 g of *S*-methylcysteine (0.0178 mol) was added. It was cooled to –50 °C and a solution of 4.9 ml of 70% *tert*-butyl hydroperoxide (0.035 mol) in toluene (10 ml) was added dropwise. It was stirred for 12 h at room temperature, the solvent was evaporated, the residue was dissolved in water and filtered. The water was evaporated in vacuo, the residue was dissolved in methylene chloride and refluxed. The precipitate was filtered off, washed on the filter with methylene chloride and recrystallized from aqueous alcohol or further purified by preparative chromatography (eluent acetonitrile-water 2:1) to yield crystalline (–)-methiin **4** (70%, 95% *ee*). M.p. 168–175 °C (decomp.); mp. 168–170 °C (decomp.) [Ref. [24] mp. 165–170 °C (decomp.)]. Ref. [24] $[\alpha]_D^{20} = -110°$ (c = 1, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 2.62 (s, 3H), 3.13 (dd, J = 14.0, 8.0 Hz, 1H), 3.22 (dd, J = 14.0, 6.0 Hz, 1H), 4.6 bs (NH_3^++H_2O). ^{13}C-NMR (125 MHz, D_2O) δ 40.2 (CH_3); 53.3 (CH); 56.1 (CH_2); 175.5 (CO_2H).

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