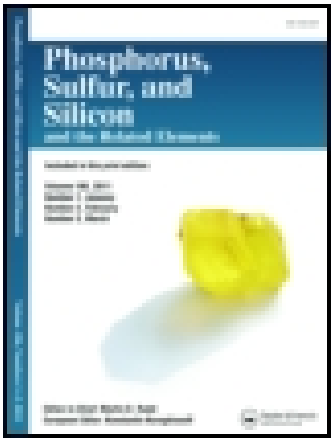

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Stereoselective Chemo-Enzymatic Approaches to the Synthesis of C_2 1,3-Dithiane-1,3-dioxide

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Two enzyme-mediated methods are presented for the preparation of enantiomerically enriched C_2 1,3-dithiane-1,3-dioxide. The first takes advantage of a trans *stereoselective oxidation by $NaIO_4$ of enantiomerically pure (R) 1,3-dithiane-1-oxide obtained by cyclohexanone monooxygenase. In the second method, a kinetic resolution consisting of a domino hydrolysis-decarboxylation process of (±) 2-carbethoxy-1,3-dithiane-*trans*-1,3-dioxide is described. The target molecule is obtained with enantiomeric excesses up to 90%.*

Keywords C_2-symmetric bis(sulfoxides); cyclohexanone monooxygenase; 1,3-dithiane-*trans*-1,3-dioxide; kinetic resolution; pig liver esterase; subtilisin Carlsberg

INTRODUCTION

C_2-Symmetric bis(sulfoxides) have attracted great interest in the last ten years for their intrinsic advantages in asymmetric synthesis. In particular, enantiopure 1,3-dithiane-*trans*-1,3-dioxide (**3**) is easily metallated at the C-2 carbon atom giving rise to a chiral carbonyl anion, which shows a high level of stereocontrol in addition reactions with aromatic aldehydes.[1–3] The resulting alcohol intermediate can be transformed into a series of α-hydroxycarbonyl derivatives, such as esters, amides, ketones, and aldehydes.[4,5] Moreover, 2-methylene 1,3-dithiane-*trans*-1,3-dioxide is synthetically equivalent to chiral ketenes in cycloadditions such as Diels–Alder reactions.[6]

The direct stereoselective titanium-catalyzed oxidation of the parent 1,3-dithioacetal (**1**) appears as the most appealing method to achieve

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.
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1,3-dithiane-*trans*-1,3-dioxide (**3**), but unfortunately it leads to an almost racemic product. In order to obtain a high enantiomeric excess, Aggarwal et al. used a two-step procedure involving the Modena-modified oxidation of 2-carbethoxy-1,3-dithiane, followed by hydrolysis and decarboxylation.[7] Moreover, in spite of good enantioselectivity, this method is time-consuming and suffers from modest overall chemical yield.

It is universally recognized that remarkable features of enzymatic methods are mild reaction conditions, high chemo-, regio- and stereoselectivity. They often lead to enantiomerically pure products; and being devoided of salts and metal waste, and at the same time realizing energy savings. In this article, we describe our studies to prepare enantiomerically enriched 1,3-dithiane-*trans*-1,3-dioxide (**3**) by chemoenzymatic methods.

RESULTS AND DISCUSSION

To the best of our knowledge, no useful biocatalytic direct bis-oxidation of 1,3-dithioacetals to the corresponding bis(sulfoxides) is reported in the literature.

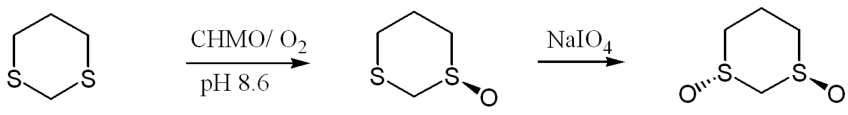
Cyclohexanone monooxygenase (CHMO) (EC 1.14.13.22) from *Acinetobacter calcoaceticus* NCIB 9871 is a NADPH-dependent flavo enzyme that is able to oxidize a wide range of alkyl aryl sulfides[8] and dialkyl sulfides[9] to the corresponding sulfoxides.

We have already shown that the monooxidation of 1,3-dithiane (**1**) to the (*R*)-monosulfoxide (**2**) with CHMO occurs with almost total enantioselectivity in high chemical yield.[10] The oxidation of **1** was performed in Tris-HCl buffer pH 8.6, containing CHMO, NADPH, and the system glucose-6-phosphate/glucose-6-phosphate dehydrogenase to regenerate the cofactor,[8] for 16 h.

Unfortunately, the use of this NADPH-dependent enzyme was limited by the necessity of recycling the expensive cofactor, which prevented its application to a multigram scale even with a membrane reactor type system. This has been overcome by some of us by using a whole-cell approach that led to the 1,3-dithiane monosulfoxide (**2**) in one gram scale.[11]

We have now envisaged a chemo-enzymatic route to enantiomerically enriched 1,3-dithiane-*trans*-1,3-dioxide (**3**).

Indeed, the straightforward addition of sodium metaperiodate to a methanol/water mixture containing the crude monosulfoxide (*R*)-**2**, obtained via enzymatic oxidation, gave C_2 (*R*, *R*)-bis(sulfoxide) **3** in 90% yield and 90% enantiomeric excess (Scheme 1). The absolute

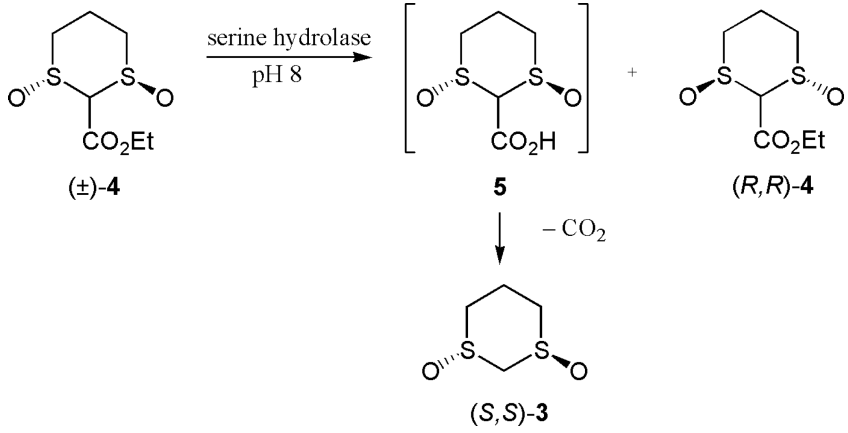


1 (*R*)-**2** (*R*, *R*)-**3**

SCHEME 1

configuration of **3** was determined by chiral HPLC comparison with a sample prepared according to the method of Aggarwal et al.[7]

Our second approach was a kinetic resolution of the starting racemic 2-carbethoxy-1,3-dithiane-*trans*-1,3-dioxide (**4**) to the corresponding acid (**5**), catalyzed by serine-hydrolases, followed by a chemical decarboxylation step via the typical domino reaction pathway (Scheme 2). Several enzyme-mediated kinetic resolutions of a variety of sulfinylcarboxylates have already been achieved by using commercially available hydrolytic enzymes.[12]



(±)-**4** **5** (*R*,*R*)-**4** (*S*,*S*)-**3**

SCHEME 2

The serine hydrolases used in this work were commercially available subtilisin Carlsberg (EC 3.4.21.14) and a crude preparation of pig liver esterase (PLE) (EC 3.1.1.1). Racemic 2-carbethoxy-1,3-dithiane-*trans*-1,3-dioxide (**4**) was obtained by oxidation of the commercial 2-carbethoxy-1,3-dithiane with *meta*-chloroperbenzoic acid, as described in the literature.[7] The enzymatic hydrolysis and decarboxylation of **4** were performed at room temperature, in sodium borate buffer pH 8, with an enzyme:substrate weight ratio of 1:1, for variable reaction times (Table I).

TABLE I Resolution of 4 Catalyzed by Serine Hydrolases

Enzyme	Time (h)	Conv[a] (%)	ee (**3**)[b] (%)
Subtilisin Carlsberg	72	20	20 (*S*, *S*)
PLE[c]	2	50	25 (*S*, *S*)

[a]Determined by ^{1}H NMR spectroscopy.
[b]Determined by HPLC.
[c]Pig liver esterase.

It is worth noting that the starting ester **4** remained unreacted in the absence of the enzyme.

Subtilisin Carlsberg gave (*S*,*S*)-**3** with an enantiomeric excess of 20% at the conversion of 20% (Table I). Therefore this enzyme afforded the opposite enantiomer to that obtained by CHMO-$NaIO_4$ oxidation.

Variations of the solvent system by the addition of organic cosolvents are quite frequently used methods to improve the selectivity of hydrolytic enzymes.[13] We have screened different organic solvents[14] in the resolutions of 2-carbethoxy-1,3-dithiane-*trans*-1,3-dioxide (**4**) catalyzed by subtilisin Carlsberg. However, we could not observe any improvement in the enantioselectivity of the reaction.

The influence of the substrate structure was also investigated. Racemic phenyl 2-carboxylate-1,3-dithiane-*trans*-1,3-dioxide (**6**), 2-carboxamide-1,3-dithiane-*trans*-1,3-dioxide (**7**), and 2-(*N*-*iso*-propyl)carboxamide-1,3-dithiane-*trans*-1,3-dioxide (**8**) were prepared. Unfortunately, none of these compounds was suitable for the protease, and only the starting material was recovered after long reaction time.

When the enzymatic hydrolysis of **4** was carried out in the presence of pig liver esterase (PLE), a fast reaction was observed, although with 25% ee (Table I).

In analogy to our results, the study of the kinetic resolution of a series of *trans* 2-alkoxycarbonyl-3,6-dihydro-2*H*-thiopyran *S*-oxides to the corresponding acids by PLE has shown that the presence of an electron-withdrawing substituent in the α position to the carboxylic functionality produced the spontaneous decarboxylation of the acid under the reaction conditions used,[12] the enantiomeric excesses not being determined.

In conclusion, resolution of (±)-2-carbethoxy-1,3-dithiane-*trans*-1,3-dioxide expands the synthetic application of hydrolytic enzymes in the field of organo sulfur compounds and opens a new route for the preparation of **3**, in spite of the modest enantiomeric excesses obtained in this work.

The CHMO-$NaIO_4$ oxidation of 1,3-dithiane (**1**) represents an easy access to the enantiomerically pure target bis(sulfoxide) **3** and competes favorably with titanium-mediated oxidation in terms of chemical yield, and mild and environmentally acceptable conditions.

EXPERIMENTAL

Melting points were determined on a BÜCHI 535 and are corrected. NMR spectra were recorded with a Bruker AC 300 or AC 200 spectrometer, operating at 300.13 or 200.13 MHz for ^1H and 75.3 or 50 MHz for ^{13}C. Coupling constants J are given in Hz. Chemical shifts are reported using $CHCl_3$ as external standard (7.24 ppm for ^1H NMR and 77.0 for ^{13}C NMR).

Chiral HPLC separations were performed on an Agilent HP 1100 apparatus, equipped with a diode array detector, and the volume of injection was 20 μL.

2-Carbethoxy-1,3-dithiane was purchased from Aldrich and used without purification. Crude lyophylized pig liver esterase (PLE) and subtilisin Carlsberg were purchased from Sigma.

Preparation of (*R*)-1,3-Dithiane-1-oxide (2) by Oxidation of 1,3-Dithiane (1) with CHMO

The dithioacetal (**1**) (0.04 mmol, 5 mg) was reacted at 25°C under magnetic stirring in 2.5 mL of 0,05 M Tris-HCl buffer, containing NADP (3.5×10^{-3} mmol, 2.7 mg), glucose-6-phosphate (0.2 mmol, 67.8 mg), 3.36 units of partially purified from *E. Coli* TOP10 strain CHMO, and 10 units of glucose-6-phosphate dehydrogenase. After 20 h, the reaction mixture was extracted with CH_2Cl_2 (4×5 mL). The combined organic extracts were dried over sodium sulfate. Removal of solvent under reduced pressure gave 4.5 mg of the title compound, yield 79%. ^1H NMR ($CDCl_3$): $\delta = 2.17$–2.27 (m, 1H), 2.50–2.71 (m, 4H), 3.32 (m, 1H), 3.64 (d, $J = 12.8$ Hz, 1H), 4.01 (d, $J = 12.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$): $\delta =$ 27.2 (CH_2), 28.2 (CH_2), 50.4 (CH_2), 52.8 (CH_2). HPLC (Chiralcel OJ-H, *i*PrOH-hexane 30–70, 0.6 mL/min, λ 220 nm), t_R (*S, S*) 12.7 min, t_R (*R, R*) 15.1 min, ee 90%. Anal. Calcd. for $C_4H_8OS_2$: C, 35.26; H, 5.92; S, 47.07. Found: C, 35.19; H, 5.91; S, 47.02%.

Preparation of (*R,R*)-1,3-Dithiane-1,3-dioxide (3) by Oxidation of (*R*)-1,3-Dithiane-1-oxide (2) with $NaIO_4$

(*R*)-1,3-dithiane-1-oxide (**2**) (4.5 mg) was dissolved in 2 mL of a 1:4 MeOH:H_2O solvent mixture. Solid $NaIO_4$ (0.05 mmol, 11 mg) was added

to the reaction mixture. After 24 h of stirring at room temperature, the mixture was extracted with dichloromethane (4 × 10 mL), and the combined organic extracts were dried over sodium sulfate. Removal of the solvent under reduced pressure gave 4.5 mg of the title compound, yield 90%. ^{1}H NMR ($CDCl_3$): $\delta = 2.70$ (m, 2H), 3.05 (m, 2H), 3.18 (m, 2H), 4.05 (s, 2H). HPLC (Chiralcel OJ-H, EtOH:hexane 40:60, 0.6 mL/min, λ 220 nm) t_R (R, R) 15.9 min, t_R (S, S) 19.5 min, ee 90%. Anal. Calcd. for $C_4H_8O_2S_2$: C, 31.56; H, 5.30; S, 42.13. Found: C, 31.46; H, 5.29; S, 42.05%.

Preparation of (*S,S*)-1,3-Dithiane-*trans*-1,3-dioxide (3) by Resolution of Racemic 2-Carbethoxy-1,3-dithiane-*trans*-1,3-dioxide (4)

Racemic 2-carbethoxy-1,3-dithiane-*trans*-1,3-dioxide (**4**) (2 mg)[7] was reacted at 25°C under stirring in 5 mL of borate buffer pH 8 in the presence of 2 mg of PLE or subtilisin Carlsberg. The reaction course was followed by TLC using AcOEt:EtOH 7:3 as eluent. When the desired degree of conversion was reached, the reaction was quenched by adding 3 mL of ethanol, and the solvent was evaporated at reduced pressure and at room temperature to avoid the spontaneous decarboxylation of the unreacted starting material. The crude reaction mixture was used without purification for ^{1}H NMR and HPLC analysis. The conversion has been determined by ^{1}H NMR spectroscopy by the ratio of two different singlets for C-2 protons of **4** and **3**. HPLC (Chiralcel OJ-H, EtOH-hexane 40–60, 0.6 mL/min, λ 220 nm) t_R (R, R) 15.9 min, t_R (S, S) 19.5 min, ee 25%. Anal. Calcd. for $C_4H_8O_2S_2$: C, 31.56; H, 5.30; S, 42.13. Found: C, 31.51; H, 5.30; S, 42.09%.

Preparation of 2-Carboxamide-1,3-dithiane

To a stirred solution of dithiane carboxylic acid[15] (1 g, 6 mmol) in anhydrous dichloromethane (50 mL) under a dry nitrogen atmosphere, one drop of dimethylformamide and dropwise thionyl chloride (0.798 g, 6.7 mmol) was added. The solution was stirred for 15 min at room temperature, and then the solvent was evaporated, affording the crude acyl chloride as a red-orange solid. This was dissolved in anhydrous dichloromethane (50 mL), and NH_3 was bubbled in for 10 min. The solution became muddy, and after chilling to 0°C, a precipitate formed. The solid material was recovered and purified by crystallization (EtOH) to give 0.82 g (yield 82%) of the title compound, mp 170–172°C.[16] ^{1}H NMR ($CDCl_3$): $\delta = 2.01$–2.19 (m, 2H), 2.69–2.81 (m, 2H), 3.05–3.19

(m, 2H), 4.41 (s, 1H), 5.71 (bs, 1H), 6.43 (bs, 1H). Anal. Calcd. for $C_5H_9NOS_2$: C, 36.78; H, 5.56; N, 8.58; S, 39.28. Found: C, 36.81; H, 5.54; N, 8.60; S, 39.31%.

Preparation of 2-(*N-iso*-Propyl)carboxamide-1,3-dithiane

The crude acyl chloride (6 mmol), obtained as described above, was dissolved in anhydrous dichloromethane (50 mL), and *N-iso*-propylamine (1 mL, 12 mmol) was added at 10°C. The mixture was stirred for 30 min at 10°C and then washed with 10 mL of saturated aqueous NaCl. The organic phase was dried and evaporated at reduced pressure to give a yellowish solid that was purified by silica gel flash chromatography using CH_2Cl_2:CH_3OH 85:15 as eluent. ^{1}H NMR ($CDCl_3$): $\delta = 1.13$ (d, $J =$ 6.8 Hz, 6H), 2.05–2.15 (m, 2H), 2.70–2.75 (m, 2H), 3.10–3.17 (m, 2H), 4.01 (m, 1H), 4.34 (s, 1H), 6.20 (bs, 1H). Anal. Calcd. for $C_5H_9NOS_2$: C, 36.78; H, 5.56; N, 8.58; S, 39.28. Found: C, 36.79; H, 5.57; N, 8.61; S, 39.28%.

Preparation of 2-Substituted-1,3-dithiane-*trans*-1,3-dioxides 6–8: General Procedure

To a stirred solution of 2-substituted-1,3-dithiane (2.5 mmol) in 7 mL of diethyl ether at 0°C, 70% *m*–CPBA (1.23 g, 5 mmol) dissolved in 12 mL of diethyl ether was added. After 1–3 h of stirring at the same temperature, the reaction was deemed complete by TLC, and the mixture was filtered through a sintered-glass funnel. The solid residue was washed with several aliquots of cold ether. The solvent was evaporated at reduced pressure, and the resulting crude was purified by flash chromatography.

Phenyl 2-Carboxylate-1,3-dithiane-trans-1,3-dioxide (6)

41%, 279 mg. AcOEt:acetone 95 :5, mp 194–195°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 2.41–2.80 (m, 2H), 3.30 (m, 1H), 3.37 (m, 1H), 3.690–3.84 (m, 2H), 5.31 (s, 1H), 7.16–7.48 (m, 5H). Anal. Calcd. for $C_{11}H_{12}O_4S_2$: C, 48.51; H, 4.44; S, 23.55. Found: C, 48.49; H, 4.43; S, 23.56%.

2-Carboxamide-1,3-dithiane-trans-1,3-dioxide (7)

The reaction has been carried out in MeOH. 34%, 166 mg. CH_2Cl_2/MeOH 92:8 to 80:20, mp 175°C. ^{1}H NMR (DMSO-d_6): $\delta = 1.88$–1.97 (m, 2H), 2.68–2.76 (m, 2H), 3.16–3.30 (m, 2H), 4.49 (s, 1H), 7.09 (bs, 1H), 7.38 (bs, 1H). ^{13}C NMR (DMSO-d_6): $\delta = 25.1$ (CH_2), 27.1 (CH_2), 43.9

(CH), 170.4 (C). Anal. Calcd. for $C_5H_9NO_3S_2$: C, 30.76; H, 4.65; N, 7.17; S, 32.84. Found: C, 30.75; H, 4.65; N, 7.19; S, 32.85%.

2-(N-iso-Propyl)carboxamide-1,3-dithiane-trans-1,3-dioxide (8)

36%, 213 mg. CH_2Cl_2:MeOH 9:1. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.11 (d, $J = 6.7$ Hz, 6H), 2.37–2.45 (m, 2H), 3.04–3.10 (m, 2H), 3.21–3.28 (m, 1H), 3.51 (ddd, $J = 2.9$, 7.5, 12.8 Hz, 1H), 3.92 (m, 1H), 4.84 (s, 1H), 8.17 (d, $J = 7.3$ Hz).^{13}C NMR (DMSO-d_6): $\delta = 14.9$ (CH_2), 22.0 (CH_3), 22.2 (CH_3), 41.4 (CH), 45.9 (CH_2), 48.4 (CH_2), 74.3 (CH), 160.9 (C). Anal. Calcd. for $C_8H_{15}NO_3S_2$: C, 40,48; H, 6.37; N, 5.90; S, 27.02. Found: C, 40.44; H, 6.36; N, 5.91; S, 27.04%.

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