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Microbiological Transformations 35: Enantioselective One-step Preparative Scale Synthesis of 1,3-dithiane-1-oxide *via* Whole-cell Bacterial Oxidation.

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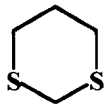
Abstract: This work describes the preparative scale enantioselective oxidation of 1,3-dithiane to the corresponding monosulfoxide using whole-cell cultures of two bacteria, i.e. *Acinetobacter calcoaceticus* NCIMB 9871 and *Pseudomonas* sp. NCIMB 9872. Copyright © 1996 Elsevier Science Ltd

Sulfoxide-stabilized carbanions have been shown over the last decades to be highly valuable building blocks and/or chiral intermediates in asymmetric synthesis.[1] In particular, the use of the monosulfoxide of prochiral 1,3-dithiane **1** (i.e. 1,3-dithiane 1-oxide **2**),[2,3] of its disulfoxide[4,5] or of their 2-substituted derivatives[2] as chiral auxiliaries has been recently developed. These chirons have been used as stereocontrol elements in the course of various synthetic transformations, and were shown to be very useful for achieving asymmetric synthesis implying for instance enolate alkylation, nucleophilic substitution, reduction, conjugate addition, cycloaddition or Mannich condensation.[2]



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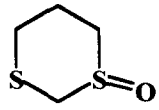

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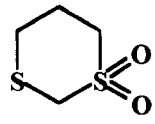

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In spite of their synthetic interest, it occurs that preparation of these chirons remains cumbersome. Thus, the direct asymmetric oxidation of **1** and of its 2-alkyl derivatives using Sharpless epoxidation reagent in Kagan's or Modena's conditions led to monosulfoxides showing only low to moderate ees (≤ 30 %).[2,5] Therefore, synthesis of optically pure 1,3-dithiane-1-oxide **2** had to be achieved *via* multistep procedures like for instance chemical separation of a diastereoisomeric D-(+)-camphor adduct of **2** followed by cleavage of the camphor moiety.[6] A more efficient method has been described recently by Page and coll. and involves: (a) acylation of dithiane, (b) oxidation using Kagan's and Modena's procedure of this acyl derivative (ee = 92 %), intermediate crystallization (ee = 100%) and (c) subsequent deacylation (40 % overall yield).[2,7] Approaches based on

microbiological oxidations allowing for the asymmetric synthesis of various chiral sulfoxides have also been described.[8] However, the only result describing oxidation of 1,3-dithiane (using whole cells of the fungi *Mortierella isabellina*, *Aspergillus foetidus* or *Helminthosporium* sp.) only led to monosulfoxide **2** showing poor ees ($0 < ee < 22$ %).[9]

Some of us have shown recently that cyclohexanone monooxygenase (CMO), an enzyme known to carry out asymmetric Baeyer-Villiger reactions[10,11] and oxidation of monosulfides,[12] was also able to achieve the highly stereoselective oxidation of some prochiral 1,3-dithioacetals.[13] Unfortunately, the use of this NADPH dependent enzyme necessitates concomitant recycling of this expensive cofactor and is therefore costly and not easy to extrapolate to multigramme scale, even with a membrane reactor type system.[14] This could be overcome using a whole-cell approach. We describe here the preparative scale oxygenation of 1,3-dithiane by a culture of two bacteria, *Acinetobacter calcoaceticus* NCIMB 9871[11] and *Pseudomonas* sp. NCIMB 9872,[15] known to contain respectively an inducible cyclohexanone or cyclopentanone monooxygenase.

RESULTS

Biotransformations of the prochiral 1,3-dithiane **1** were carried out using 1 L cultures of either strain after 15-20 h growth. The carbon sources used, supposed to induce the biosynthesis of the corresponding monooxygenases, were cyclohexanediol or cyclopentanol respectively (1.5 g/L). In these conditions,[16] oxidation of 1 g of **1** (solubilized in 10 mL EtOH) led to the formation of two products: i.e. monosulfoxide **2** and the corresponding monosulfone **3**, as shown in the Table below. These products were identified by comparison with their previously described spectroscopic data,[2,7,17] and their absolute configuration were determined on the basis of the sign of their optical rotation, these configurations having been unambiguously determined by X-Ray crystallography.[6]

Microorganism	**Reaction time**	**Sulfoxide 2**					**Sulfone 3**
		yield [a]	$[\alpha]_D^{21}$ [b]	o.p.[c]	e.e.[d]	abs. conf. [c]	yield [a]
A. calcoaceticus	2 h 45	76 %	+ 210	≥ 98 %	98 %	(*R*)	20 %
Pseudomonas sp.	8 h	85 %	- 130	60 %	57 %	(*S*)	5 %

Bacterial oxidation of 1,3-dithiane 1: (a) isolated yield; (b) c = 1, CH_2Cl_2; (c) litt[7]: enantiopure (*S*)-sulfoxide **2**: $[\alpha]_D^{20}$ = -210 (c=0.97 CH_2Cl_2); (d) determined by chiral HPLC (Chiralcel OD column, iPrOH/Hexane : 25/75, (*S*)-sulfoxide: t_R = 14 min, (*R*)-sulfoxide: t_R=16 min).

Interestingly, these results indicate that oxidation of **1** by *A. calcoaceticus* afforded (*R*)-**2**, which was obtained with a good yield and an excellent enantiomeric purity, whereas oxidation by the *Pseudomonas* sp. strain led to the opposite (*S*) enantiomer, showing that these bacteria were enantiocomplementary. Using these

conditions, formation of some monosulfone **3** was observed in both cases whereas no disulfoxide was detected. The kinetic course of these biotransformations is detailed in Fig. 1 and 2. It can be observed that, in the case of biotransformation by *A. calcoaceticus*, a first - stereoselective - oxidation of **1** led to sulfoxide **2** showing an ee of 82 %. This oxidation occurred exclusively as long as some substrate remained in the reaction medium. After disappearance of **1**, a second oxidation of **2** into **3** took place further on and led to increase the enantiomeric purity of **2** up to 98 %. This indicates that this second oxidation is *enantioselective*; the minor (*S*) enantiomer of **2** being oxidized faster than the major (*R*) enantiomer. This phenomenon had also been observed with the purified monooxygenase[13] indicating that no other enzyme was implied. A similar kinetic resolution has been described elsewhere with the use of chemical catalysts.[18,19] In the case of *Pseudomonas* sp., this second oxidation was only weakly enantioselective, resulting in a slight decrease of the ee of **2** (from 57 % ee for 0 % sulfone formation to 50 % ee for 20 % sulfone formation). Apparently, the major (*S*) enantiomer is again oxidized slightly faster than its antipode.

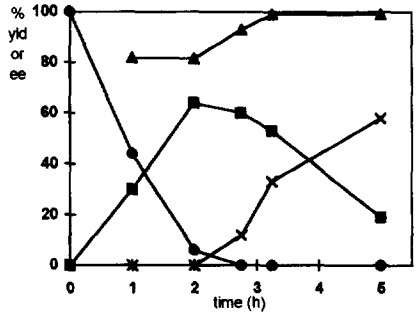

Figure 1

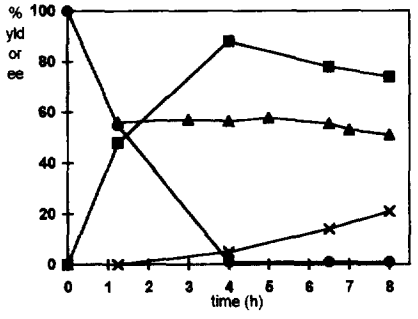

Figure 2

Figures 1 and 2: Kinetical course of the oxidation of **1** by *A. calcoaceticus* (Fig.1) and *Pseudomonas* sp. (Fig.2)
● dithiane (yield) ■ sulfoxide (yield) ▲ sulfoxide (ee) × sulfone (yield)

It is interesting to emphasize that the absolute configuration of the sulfoxide obtained with *A. calcoaceticus* is in perfect agreement with the prediction which could have been made on the basis of the previously published active site model of its cyclohexanone monooxygenase.[12] Placing the "non-oxidized" sulfur atom in the so-called M pocket of this model, and considering oxygen transfer from the top as proposed by these authors, leads to predict formation of the (*R*)-antipode which is obtained indeed. With this strain, oxidation of the minor (*S*)-**2** enantiomer into **3**, being due to the same enzyme,[13] occurred from the same direction. Surprisingly, this is not the case with *Pseudomonas* sp., where the second oxidation occurs preferentially from the opposite side as compared to the first one. This may be due to an other enzyme or to positioning variations in the same active site for instance. At the present time, we do not have any argument favouring one or another hypothesis. The E values of these two "second oxidations" are approximately 13 (for

A. calcoaceticus) and 2 (for the *Pseudomonas* sp.) showing that this approach could not be used for the efficient resolution of the racemic sulfoxide. Also, these oxidations are relatively slow.

In conclusion, these results emphasize the fact that both enantiomers of 1,3-dithiane-1-oxide **2** can be prepared in enantiomerically enriched form using a single step procedure. In particular the (*R*)-antipode can be readily obtained in good yield and excellent ee (> 98 %). The biotransformations using whole-cell cultures of these two bacteria avoid the problems linked to the use of the corresponding purified monooxygenases and thus appear well appropriated to preparative scale extrapolation. We are currently studying sulfoxidation of other thioacetals and thioketals with various microorganisms known to carry out Baeyer-Villiger oxidations in order to offer a complement to the conventional chemical approaches.

Acknowledgements

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