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Enantio- and Diastereoselective Synthesis of Erysulfone and Erysulfoxide

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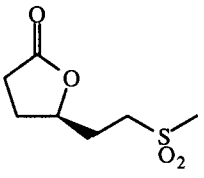
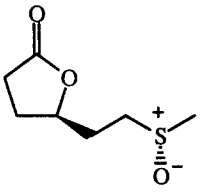
Abstract: The natural products erysulfone (**1**) and erysulfoxide (**2**) have been prepared from (+)-muconolactone (**3**). This synthetic work has substantiated the earlier, probable assignment of absolute configuration of these targets. © 1997 Elsevier Science Ltd.

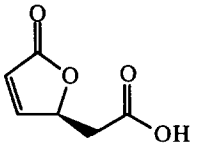
The unusual sulfur-containing butanolide natural products erysulfone (**1**) and erysulfoxide (**2**) have been isolated, in small quantities, from the fruits of the flowering perennial *Erysimum inconspicuum* by Piatak *et al.*.[2] Both compounds, although the sulfoxide in particular, have high cytotoxic activities against cancer cell lines and hence make interesting targets for asymmetric synthesis.



(**1**)



(**2**)



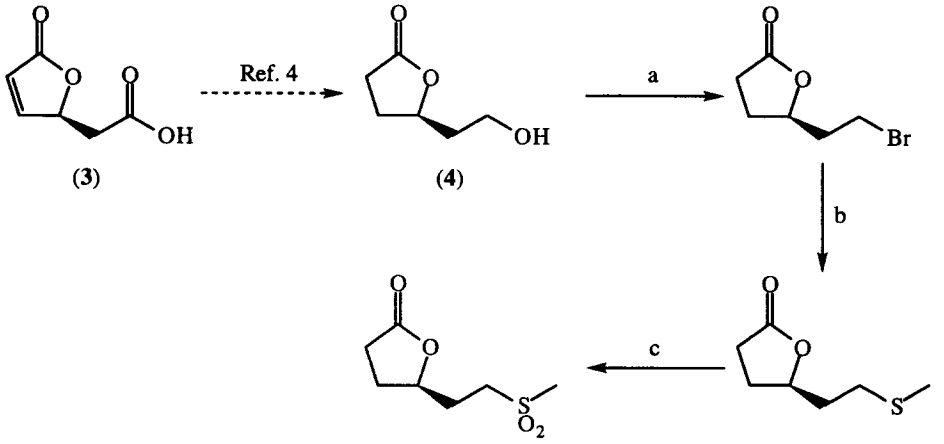
(**3**)

The C-5 chiral centre in **1** has been given a probable, although not unequivocal, assignment of (R) configuration by single crystal *X*-ray characterization, while the sulfoxide moiety in **2** was assigned as (S) on the basis of correlation of the optical rotation with those of methyl-n-butylsulfoxide and 5-methylsulfinylpentylisocyanate.[3]

We have been investigating the synthetic applications of (+)-muconolactone (**3**), which can be obtained in high yield and enantiomeric excess by the biotransformation of both enantiomers of racemic mandelate by a mutant strain of the bacterium *Pseudomonas putida*.[4] This compound was originally held to have (5S) configuration on the basis of a sequence of chemical and enzymatic degradations[5] but this assignment was called into question by CD correlation studies on the corresponding methyl ester.[6] However subsequent convergent synthetic work by Bloch *et al.*,[7] further corroborated by us,[4] has unambiguously confirmed the original (5S) assignment. Indeed Gawronski *et al.* have since reinterpreted the CD results as part of a broader study of similar compounds.[8]

(+)-Muconolactone therefore seemed an ideal starting point for the synthesis of **1** and **2** both in terms of absolute configuration and of side chain length and functionality and we were gratified to be able to prepare **1** in a straightforward fashion (Scheme 1). Thus the alkene and acid functionalities of **3** can be reduced, as we have described before,[4] to give the fully saturated alcohol **4**. After bromination of this alcohol,[9] the sulfur

containing side chain can be introduced by simple nucleophilic substitution followed by oxidation to give erysulfone. Comparison of the optical rotatory dispersion spectrum of our synthetic material ($[\Phi]_{600}$ -110.00, $[\Phi]_{589}$ -116.67, $[\Phi]_{500}$-176.00, $[\Phi]_{400}$ -290.00, $[\Phi]_{300}$ -620.00) with that reported for the original isolate ($[\Phi]_{600}$ -75.79, $[\Phi]_{589}$ -75.79, $[\Phi]_{500}$-113.68, $[\Phi]_{400}$ -189.47, $[\Phi]_{300}$ -530.51)[2] showed close agreement and confirmed that erysulfone does indeed have (5R) configuration.[10]



(3) (4)

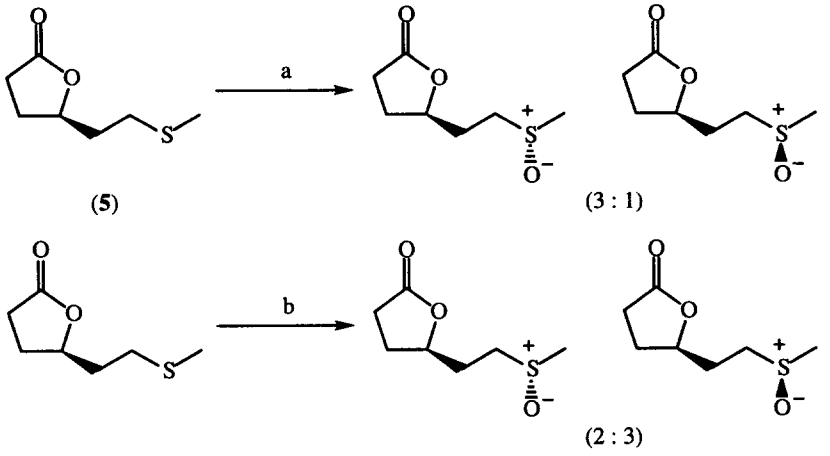
a) $Ph_3P.Br_2$, pyridine, CH_2Cl_2 (79%); b) MeSNa, THF (75%);
c) aq. H_2O_2, cat. H_2WO_4 (42%)

Scheme 1

Our approach to erysulfoxide rested on the use of the Kagan asymmetric sulfoxidation procedure,[11] where we were encouraged by the fact that this protocol had shown moderate diastereoselectivity in the oxidation of methylthiomethyloxiranes.[12] In our system (Scheme 2), the use of (-)-diethyl tartrate as the titanium ligand (which precedence[11,12] indicated would favour the formation of the (S) sulfoxide) gave the two diastereoisomers in a ratio of *ca.* 3:1[13] - similar to the methylthiomethyloxirane example. Oxidation in the presence of (+)-diethyl tartrate produced opposite diastereoselectivity with a product ratio of *ca.* 2:3 favouring what we presume to be the (R) sulfoxide. This lower ratio presumably reflects a less favourable matching of the chiral centres in the ligand and that extant in the substrate.

The ORD spectra of these two sulfoxide diastereomeric mixtures are not amenable to direct interpretation. However, in the knowledge of the relative amount of each component present, comparison of these two sets of data (together with that for the 1:1 mixture of sulfoxides that could be obtained by interupting the H_2WO_4 catalyzed oxidation used to produce the sulfone) allows deconvolution of the contribution of each of the diastereoisomers to the overall measurement at each wavelength. This analysis reveals a positive ORD curve for the (S) sulfoxide - in common with that of the natural product - and a negative curve for the (R) diastereoisomer. Thus, if we assume that the Kagan oxidation has behaved according to the examples reported

to date in the literature, the absolute configuration of the sulfoxide moiety in natural erysulfoxide is confirmed as being (S).



a) $Ti(OiPr)_4$, (-)-diethyl tartrate, ^tBuOOH, CH_2Cl_2 (25%);
b) $Ti(OiPr)_4$, (+)-diethyl tartrate, ^tBuOOH, CH_2Cl_2 (19%)

Scheme 2

In conclusion, we have prepared the naturally occurring forms of erysulfone and erysulfoxide from (5S)-(+)-muconolactone. In addition to providing a workable synthetic route to these unusual biologically active species, this has allowed us to confirm the earlier, somewhat tentative, assignments of absolute configuration both at the ring substitution position and at the sulfoxide moiety.

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   b) Note than many papers in this area employ a butenolide numbering system, where the chiral centre is at the 4-position.
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10. Note that in this synthetic sequence, (5S)-muconolactone will give (5R)-erysulfone.
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13. We were able to determine the relative amount of the two diastereomeric sulfoxides by integration of the peaks corresponding to the methyl groups in the 1H NMR spectrum: the S sulfoxide methyl group appeared at 2.63 ppm, that of the diastereoisomer at 2.61.

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