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DIASTEREOSELECTIVE OXIDATION OF MERCAPTURATES TO MERCAPTURATE SULFOXIDES

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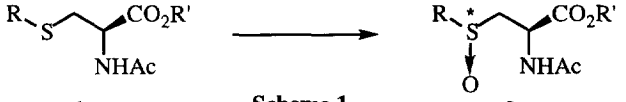
Abstract: An efficient and highly diastereoselective synthesis of mercapturate sulfoxides **2** based on the substrate contorolled asymmetric S-oxidation has been accomplished.

In the course of our ongoing projects in the search of the metabolites of antiinflamatory drug DUP 697,[1] we have isolated the mercapturic acid S-oxide from the bile of rat. The occurrence of chiral sulfoxides in the metabolic pathway of glutathione conjugation[2] and the needs not only for identification of the absolute structure but also for their biological tests prompted us to develop an efficient methodology for the preparation of enantiomerically pure mercapturic acid sulfoxides **2** (R'=H). We report here that the oxidation of the mercapturates **1** to the corresponding sulfoxides **2**[3] proceeds with unprecedently high diastereoselectivity via the 1,3-asymmetric induction[3a] employing a chirality of cysteine.[4] (Scheme 1)

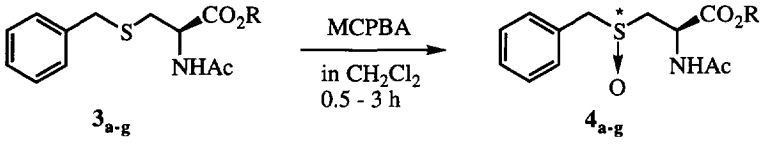


1 **Scheme 1** **2**

To evaluate an asymmetric induction during the oxidation of the mercapturates **3** to the sulfoxide **4**, we initially examined the effect of the alkyl part (R) of ester in **3**. Treatment of (+)-N-acetyl-S-benzyl-L-cysteine methyl ester $\mathbf{3_a}$[5] with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 at -50 °C provided the corresponding sulfoxide $\mathbf{4_a}$ in 87 % yield as a chromatographically separable 1:1 mixture of diastereoisomers. (Run 1) However, changing the methyl to benzyl, a slight diastereoselectivity (17 % de) was observed. (Run 2) Encouraged by this result, we next searched for more effective alkyl groups on the diastereoselection. Of these, methoxyethoxymethyl (MEM) ester $\mathbf{3_c}$[6] proved to be the best of choice. (Run 3) When the reaction was carried out at -78 °C, higher selectivity (91 % de) of $\mathbf{4_c}$[7] could be achieved. (Run 4) The use of CH_2Cl_2 as the solvent is indispensable for the oxidation since the reactions in THF or DMF did not result in any diastereoselectivities. To check the necessity of oxygen atoms in the MEM group, three substrates $\mathbf{3_{d\text{-}f}}$ were

oxidized to **4d-f** by the same reaction conditions. (Run 5-7) It was thus clarified that the oxygen of terminal methoxy goup should be essential for the appearance of higher diastereoselectivity. (Table 1)

Table 1



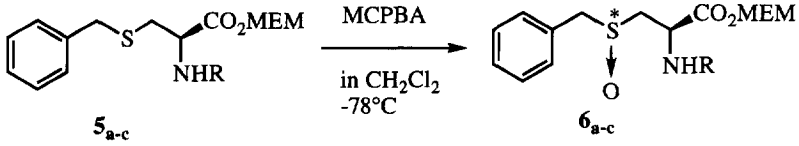
3_{a-g} 4_{a-g}

Run	3	R	Temp. °C	Yield of 4, %	de, %
1	a	Me	-50	87	0
2	b	$PhCH_2$	-50	92	17
3	c	MEM *	-50	91	82
4	c	MEM	-78	95	91
5	d	$(CH_2)_4OMe$	-50	90	71
6	e	$CH_2O(CH_2)_3Me$	-50	73	9
7	f	$(CH_2)_5Me$	-50	88	0
8	g	CH_2OCH_2Ph	-50	91	5

* MEM = $CH_2O(CH_2)_2OMe$

The influence of the protecting group on nitrogen on the diastereoselection was subsequently examined. Treatment of the MEM esters **5a-c** with MCPBA in CH_2Cl_2 at -78 °C, the sulfoxides **6a-c** were obtained in 50-87 % de. From these experiments, the acetamide functionality[8] was found to be the best for the conversion. (Table 2)

Table 2

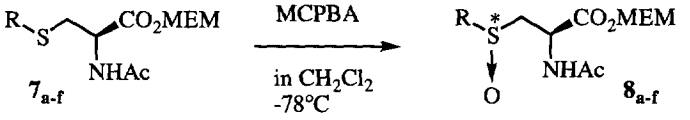


5_{a-c} 6_{a-c}

Run	5	R	Yield of 6, %	de, %
1	a	CO^tBu	92	50
2	b	$CO_2{}^tBu$	92	71
3	c	CHO	90	87

In an analogous manner, a variety of the MEM mercapturates $\mathbf{7_{a\text{-}f}}$ undergo diastereoselective oxidation promoted by MCPBA. In the examples shown below in Table 3, the *p*-nitrophenyl substituent on the sulfur slightly decreases the diastereoselectivity.

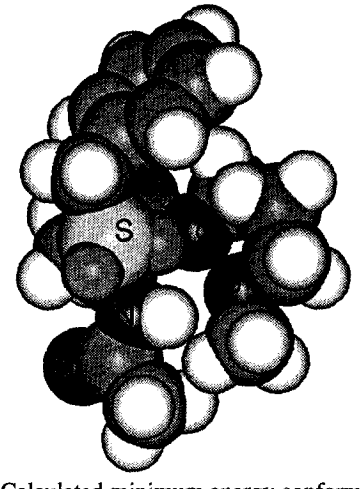
Table 3



Run	7	R	Yield of 8, %	de, %
1	a	cyclopentyl	92	86
2	b	n-hexyl	92	88
3	c	1-adamantyl	88	89
4	d	phenyl	87	67
5	e	*p*-nitrophenyl	93	60
6	f	n-propyl*	75	75

* The reaction was carried out at -50 °C.

To consider a mechanism of the diastereoselection and to predict the absolute configuration at sulfur chiral center, molecular mechanics calculations are applied to the conformational analysis of $\mathbf{3_c}$. With use of the program Discover (BIOSYM/MSI, Inc.) with the CVFF forcefield, the most stable conformational arrangement could be accessible as shown in Figure 1. Oxidation would take place preferentially on one of the lone pairs exposed to the open space over the other one, which was shielded by virtue of the MEM moiety, and should lead selectively to one diastereoisomer, whose absolute configuration at sulfur center could be deduced to be *R*. In fact, the predicted *R* configuration was eventually confirmed by X-ray crystallographic analysis of the dicyclohexylamine salt of carboxylic acid **9**[9,10], which was prepared from **8f** by sequential treatment with $ZnBr_2$ and the amine. (Figure 2)



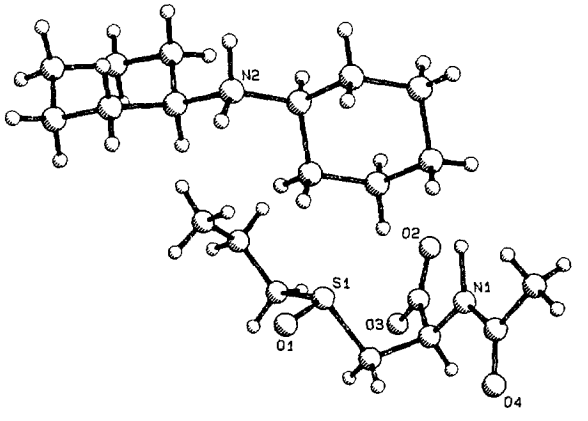


Fig.1 Calculated minimum energy conformation for $\mathbf{3_c}$. Fig.2 X-ray structure of the salt of carboxylic acid **9**.

Finally, attempted hydrolytic removal of the MEM protecting group with 3N-hydrochloric acid in THF resulted in the formation of enantiomerically pure sulfoxide **4** (R=H) in 71 % yield after recrystallization.

Thus, we have developed a convenient procedure for the preparation of chiral mercapturic acid sulfoxides, one of the important metabolites in glutathione conjugation, by a substrate controlled diastereoselective sulfur oxidation.

Acknowledgement: We thank Dr. Y. Kurogi, Otsuka Pharmaceutical Factory, Inc., for the calculations.

References and Notes

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6. All new compounds gave satisfactory spectral and analytical (combustion and/or high resolution mass spectral) data consistent with the structures shown.
7. **4c**: M.p. 94-96 °C; $[\alpha]_D$ -33° (c=0.54, MeOH); IR (KBr) ν 3292, 1754, 1660, and 1542 cm^{-1}; ^{1}HNMR (270 MHz, $CDCl_3$) δ 1.96 (3H, s), 3.06 (1H, dd, J=13.5 and 3.9 Hz), 3.25 (1H, dd, J=13.5 and 7.0 Hz), 3.36 (3H, s), 3.51-3.60 (2H, m), 3.70-3.81 (2H, m), 4.04 (2H, s), 4.88-4.98 (1H, m), 5.37 (2H, s), 7.16 (1H, d, J=7.6 Hz), 7.25-7.41 (5H, m); MS (*m/z*) 358 (M^++1).
8. On exposure of the N-methyl derivative of $\mathbf{3_c}$ to the same reaction conditions, the corresponding sulfoxide was obtained only in 9 % de in 87 % chemical yield.
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10. The salt **9**, purified by recrystallization, showed the specific rotation of $[\alpha]_D$-17° (c=0.16, H_2O) {lit.[9] $[\alpha]_D$-80° (c=1.5, H_2O)} and the enantiopurity was established as >99 % by HPLC analysis with CHIRALCEL OB-H.

    Crystallographic data for the salt **9**: m.p. 171-172 °C (lit.[9] m.p. 166 °C). A colorless plate crystals was mounted on a glass fiber. All measurement were made on a Rigaku AFC5S diffractometer with graphite monochromated Mo-Kα radiation using the ω-2θ scan technique to a maximum 2θ value of 50.1°. Cell constants are a=10.145(2), b=10.486(2), c=5.369(1) Å, α=93.45(2), β=99.22(2), γ=92.84(1)°, Z=1. All calculations were performed using the TEXSAN (TEXSAN-TEXRAY Structure Analysis Package, Molecular Structure Corporation, 1985) for 1341 unique reflections and final R factor is 0.047 (Rw=0.052). The absolute configuration of the chiral sulfoxide was determined as *R*, which was based on the stereochemistry of the L-cysteine. The refined fractional atomic coordinates, the bond lengths, the bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

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