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ENANTIOSELECTIVE TOTAL SYNTHESIS AND STRUCTURE DETERMINATION OF THE MERCAPTURIC ACID SULFOXIDE CONJUGATE

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Abstract: A practical and enantioselective total synthesis of the mercapturic acid sulfoxide **4**, a metabolite of anti-inflammatory drug DUP 697 **1**, has been accomplished by employing the substrate-controlled diastereoselective oxidation of the sulfide **7** to the sulfoxide **8** as the key step. This led to the structure determination of **4**. © 1997 Elsevier Science Ltd.

We have recently described the syntheses of the *S*-thienylmercapturic acid **2**[1] and the *O*-glucuronide **3**,[2] which were isolated from the bile of rats as the metabolites of anti-inflammatory drug DUP 697[3] possessing cyclooxygenase II inhibitory activity.[4] During the course of the project, we have also isolated the mercapturic acid sulfoxide conjugate **4** along with **2** and **3** in trace amount as a mixture of two diastereoisomers in a ratio of 7:3.[5] The structure of **4** was deduced as shown in Fig. 1 mainly on the analysis of mass spectral data.[6] However, the absolute configuration at the sulfur stereogenic center of the sulfoxide functionality in the major diasteroisomer still remains to be established. For not only the evaluation of the potential biological activity but also the elucidation of the absolute stereostructure of **4**, the development of a practical and enantiocontrolled synthetic route to this molecule was strongly desired. (Fig. 1)

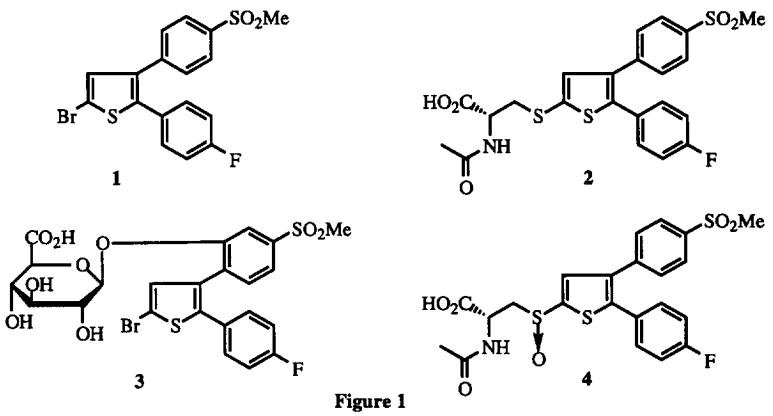
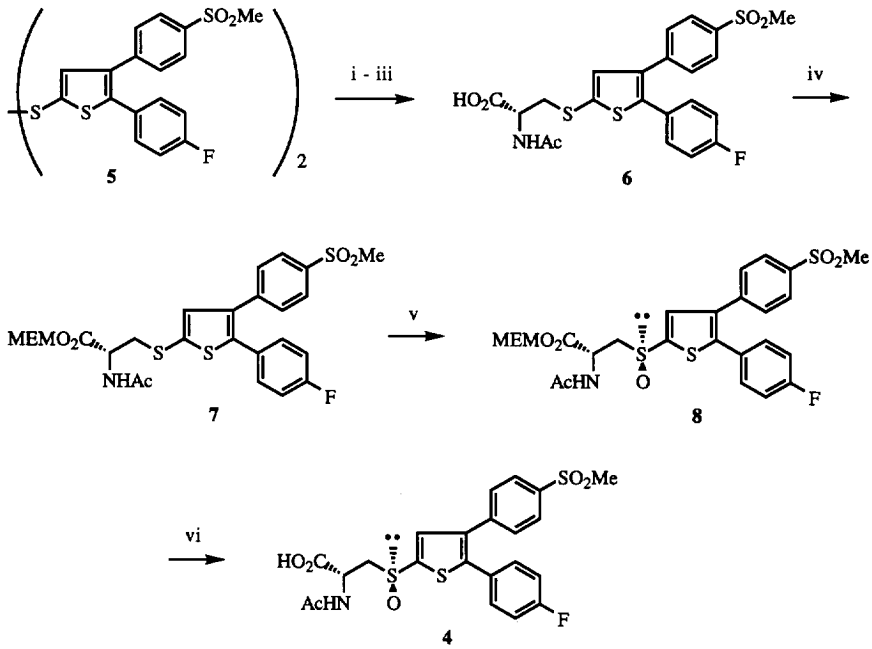


Figure 1

In this paper, we wish to report an efficient and enantioselective total synthesis of **4**, thereby establishing its absolute stereostructure, based on the substrate-controlled diastereoselective *S*-oxidation strategy recently developed in our laboratories.[7]

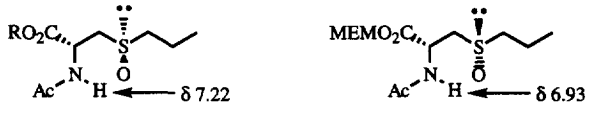
The synthesis was commenced with the enantiomerically pure *S*-thienylmercapturic acid **6**, which was prepared by utilizing a concise Mitsunobu-type coupling reaction[8] between the disulfide **5** and Boc-L-Ser-OMe via a three-step sequence of reactions. Treatment of **6** with methoxyethoxymethlyl (MEM) chloride in the presence of Hünig base[9] provided in 82% yield of the MEM ester **7**, which was then oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane at -78°C to give the sulfoxide **8** as a chromatographically inseparable biased mixture of two diastereoisomers in a ratio of 8.0:1 (from the ^{1}H-NMR). Since the diastereomeric mixture thus obtained fortunately crystallized, a recrystallization from CH_2Cl_2-Et_2O afforded the enantiomerically pure sulfoxide **8**[10] in 68% yield.



Scheme 1. ***Reagents and Conditions***: i, Boc-L-Ser-OMe, ^{n}Bu$_3$P, THF, room temp., 68%; ii, 4N-HCl, AcOH, 100°C, 77%; iii, Ac_2O, Et_3N, Et_2O-H_2O, 0°C, 91%; iv, MEMCl, ^{i}Pr$_2$NEt, DMF, room temp., 82%; v, *m*-CPBA, CH_2Cl_2, -78°C, 68%; vi, $ZnBr_2$, CH_2Cl_2, room temp., 83%.

The absolute configuration at the newly generated sulfur stereogenic center was elucidated to be *S* by careful comparison of the ^{1}H-NMR spectrum with those of the precedents. Thus, the chemical shift of a NH proton for the major diastereoisomer in the ^{1}H-NMR of **8** appears at δ 6.93, while in the minor one it appears at δ 6.80 in an integral ratio of 8.0:1. Distinct differences and similar tendencies in the chemical shifts between the two diastereoisomers were observed not only for the *n*-propyl analog **9**; the NH protons for the major **9a** and the minor diastereomer **9b** appear at δ 7.22 and δ 6.93, respectively, in a ratio of 6.4:1, but also

for other analogous derivatives described in the previous paper.[7] Since the absolute stereostructure of **9a** was unambiguously established by X-ray crystallographic analysis of the corresponding carboxylic acid **9c**, the absolute configuration at the sulfur chiral center in **8** was determined to be *S*. (Fig. 2)



9a R=MEM
9c R=H

9b

Figure 2

Finally, selective deprotection of the MEM moiety in **8** was cleanly achieved by treatment with zinc bromide[11] in dichloromethane at room temperature for 14h to produce the requisite mercapturic acid sulfoxide **4**[12] in 83% yield. It should be mentioned that the reaction conditions for the removal of the MEM group utilizing zinc bromide would be desirable, since the alternative conditions, 3N-HCl in THF at room temperature, resulted in partial epimerization at the sulfur stereogenic center in the conversion of **9a** to **9c**. The sulfoxide **4** thus prepared, $[\alpha]_D^{24}$ +4.5° (c=0.51, MeOH), was completely identical with the metabolite obtained from the bile of rats by utilizing LC-MS/MS techniques. (Scheme 1)

Thus, we have completed efficiently the total synthesis of the mercapturic acid sulfoxide **4**, a metabolite of anti-inflammatory drug DUP 697, by employing the MEM ester-directed diastereoselective oxidation as the key reaction step. In addition, the absolute configuration at the sulfur stereogenic center was determined to be *S*.

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References and Notes

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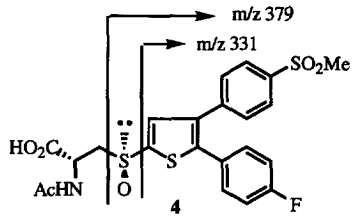
5. The ratio of the metabolite **4** was determined by measuring the peak areas of the product ion chromatograms at m/z 379 and m/z 331 (precursor ion $[M-H]^-$ m/z 508), shown below, employing the LC-MS/MS selected ion monitoring technique.



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6. Mass spectral data of **4**: Positive FABMS, molecular ion species; m/z 510 $[M+H]^+$, 532 $[M+Na]^+$, 554 $[M+2Na-H]^+$. Negative FABMS, molecular ion species; m/z 508 $[M-H]^-$, 566 $[M+NaCl-H]^-$. B/E linked scan of m/z 379, fragment ion; m/z 331.

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10. The sulfoxide **8**: m.p. 136-138 °C; $[\alpha]_D^{24}$ -9.1° (c=0.61, MeOH); IR (KBr) cm^{-1} 1742, 1656, 1312, 1056; ^1H-NMR (CD_2Cl_2) δ 2.01 (3H, s), 3.32 (3H, s), 3.51 (3H, s), 3.48-3.70 (4H, m), 3.72-3.85 (2H, m), 4.95-5.06 (1H, m), 5.39 (2H, s), 6.82 (1H, d, J=7.9 Hz), 7.00-7.12 (2H, m), 7.20-7.33 (2H, m), 7.44 (2H, d, J=8.3 Hz), 7.55 (1H, s), 7.85 (2H, d, J=8.3 Hz); MS (m/z) 597 $(M+H)^+$; Anal. Calcd for $C_{26}H_{28}FNO_8S_3$: C, 52.25; H, 4.72; N, 2.34. Found: C, 51.92; H, 4.75; N, 2.26.

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12. m.p. 185-187 °C (decomp.); $[\alpha]_D^{24}$ +4.5° (c=0.51, MeOH); IR (KBr) cm^{-1} 1740, 1652, 1312, 1016; ^1H-NMR (CD_3OD) δ 2.00 (3H, s), 3.12 (3H, s), 3.50 (1H, dd, J=10.1 and 13.2 Hz), 3.78 (1H, dd, J=4.0 and 13.2 Hz), 7.07-7.18 (2H, m), 7.30-7.41 (2H, m), 7.53 (2H, d, J=8.7 Hz), 7.76 (1H, s), 7.90 (2H, d, J=8.7 Hz); MS (m/z) 510 $(M+H)^+$; Anal. Calcd for $C_{22}H_{20}FNO_6S_3 \cdot 1/2H_2O$: C, 50.95; H, 4.08; N, 2.71. Found: C, 51.23; H, 4.07; N, 2.73.

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