A GENERAL AND EFFICIENT SYNTHESIS OF OPTICALLY PURE *S*-ARYLMERCAPTURATES

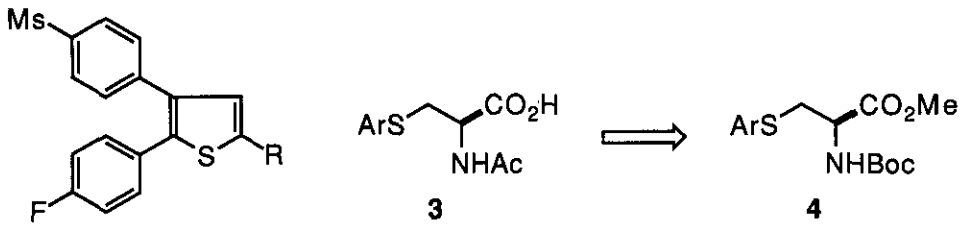
Shizuo Nakamura,* Mitsuyoshi Kondo, Kiyoto Goto, Shinsaku Naito, Yoshiaki Tsuda, and Kozo Shishido†*

Otsuka Pharmaceutical Factory, Inc., Drug Metabolism Research, Naruto, Tokushima 772, Japan

†Institute for Medicinal Resources, University of Tokushima, Sho-machi 1, Tokushima 770, Japan

Abstract - Optically pure *S*-arylmercapturate derivatives (**4**$_{a-d}$) were efficiently synthesized *via* the reaction of Boc-L-Ser-OMe (**6**) with a variety of disulfides (**5**$_{a-d}$) in the presence of tri-n-butylphosphine. The procedure was successfully applied to the synthesis of the enantiomerically pure *S*-thienylmercapturic acid (**2**), a metabolite of antiinflammatory drug DUP697 (**1**).

Mercapturic acid (**3**), aromatic *S*-substituted derivative of *N*-acetyl-L-cysteine, is one of the important metabolites in glutathione conjugation,[1] which has been considered as a major detoxication pathway in drug metabolism.[2] During the course of our study concerning the metabolic pathway of antiinflammatory drug DUP697 (**1**),[3] we intended to synthesize the *S*-thienylmercapturic acid (**2**),[4] one of the metabolites of **1**, not only as an authentic standard but also as a cytotoxic candidate.[5] To date, the efficient methods for synthesizing optically pure *S*-arylmercapturic acids[6a-c] including *S*-thienyl derivatives[6d] are few. In this communication, we wish to report a general and efficient access to *S*-arylmercapturate derivative (**4**), an intermediate of **3**, and a concise synthesis of **2** in enantiomerically pure forms. (**Figure 1**)



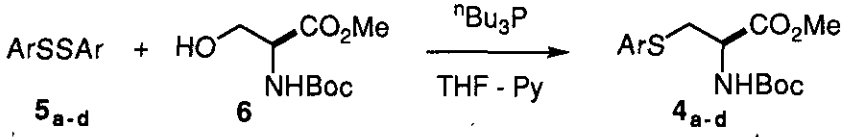
1 R=Br
2 R=*N*-Ac-Cys

3 **4**

Figure 1

Initial efforts to explore an efficient procedure for obtaining **4**, which would readily be converted into the corresponding mercapturic acid (**3**), was focused upon the coupling of *Boc-L-Ser-OMe* (**6**)[7] *with an arylthio component.* The reaction was carried out under Mitsunobu conditions[8] using thiophenol, triphenylphosphine, diethyl azodicarboxylate and Boc-L-Ser-OMe (**6**) in THF to give the desired *S*-phenylmercapturate ($\mathbf{4_a}$) (99 %ee) only in 17 % yield. The lower yield was not improved even by changing the reaction conditions. However, large enhancement of coupling yields was obtained for all four mercapturate derivatives ($\mathbf{4_{a\text{-}d}}$) by using the procedure developed by Hata.[9] On exposure of **6** to 2 eq. of disulfides ($\mathbf{5_{a\text{-}d}}$) in the presence of tri-n-butylphosphine, coupling reaction smoothly occurred to provide the corresponding mercapturate derivatives ($\mathbf{4_{a\text{-}d}}$) with high ee in good yields. When the reaction was carried out in a mixture of THF-pyridine (1:1), the best yield and ee were achieved. It should be noted that a loss of the optical purity in **6** was not observed during the conversion. **(Table 1)**

Table 1. Synthesis of Methyl S-Arylmercapturate derivatives ($\mathbf{4_{a\text{-}d}}$)

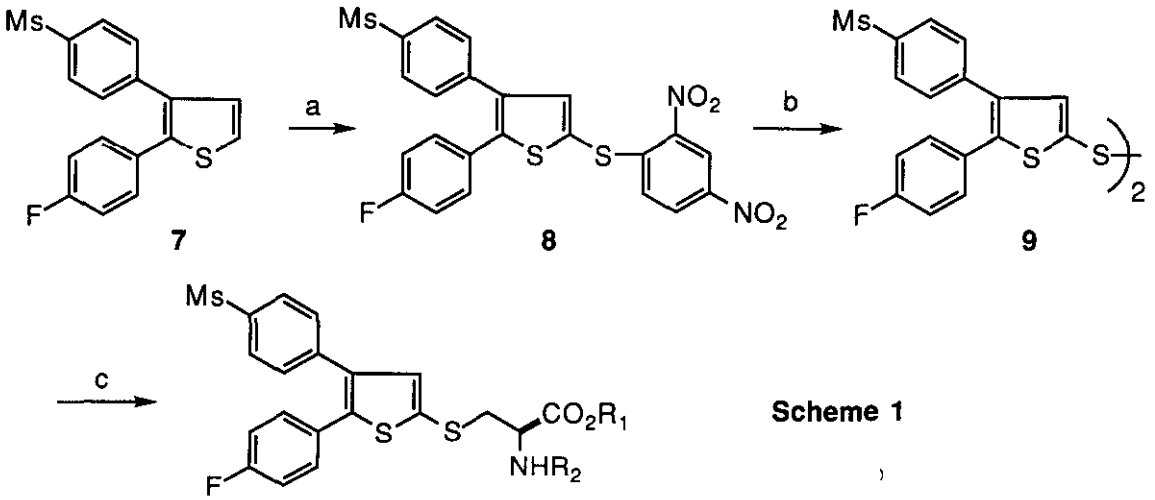


$\mathbf{5_{a\text{-}d}}$ **6** $\mathbf{4_{a\text{-}d}}$

Run	Ar	Product	Yield, % [a]	ee, % [b]
1	Ph	$\mathbf{4_a}$	75	99
2	4-MeC_6H_4	$\mathbf{4_b}$	71	98
3	4-$MeOC_6H_4$	$\mathbf{4_c}$	81	98
4	4-ClC_6H_4	$\mathbf{4_d}$	89	99

[a]Isolated yields. [b]Determined by hplc with chiral column.[13]

With an efficient method for the direct preparation of *S*-arylmercapturates in hand, we turned our attention to synthesize the mercapturic acid (**2**). Treatment of (**7**)[3] with 2,4-dinitrobenzenesulfenyl chloride in refluxing trifluoroacetic acid[10] afforded the sulfide (**8**), which was then sequentially hydrolyzed and oxidized with iodine to provide the disulfide (**9**) in 50 % overall yield. The disulfide (**9**) thus obtained was exposed to the same conditions as used for **5** to produce the mercapturate (**10**) in 68 % yield.[11] Finally, the amino acid (**11**), derived from **10** by acidic hydrolysis, was converted into the requisite mercapturic acid (**2**), whose spectral data supported the structure.[12] The optical purity of **2**, after recrystallization from ethyl acetate - diethyl ether, was determined to be 100 %ee.[13] **(Scheme 1)**



Scheme 1

Reagents and Conditions : a, 2,4-$(NO_2)_2C_6H_3SCl$, TFA, reflux, 75%; b, aq. NaOH, MeOH, reflux then I_2, MeOH, 67%; c, Boc-L-Ser-OMe, $^nBu_3P$, THF, room temperature, 68%; d, 4N-HCl, AcOH, 100 °C, 65%; e, Ac_2O, Et_3N, Et_2O, H_2O, 0 °C, 91%.

In summary, we have presented a facile method for the preparation of enantiomerically pure *S*-arylmercapturates. The procedure proved to be applicable to the synthesis of *S*-thienylmercapturic acid (**2**), a metabolite of an antiinflammatory drug DUP697 (**1**).

ACKNOWLEDGEMENT

We thank Mrs. Y. Yoshioka of our Faculty for mass spectral measurements.

REFERENCES

1. L. F. Chasseaud, " Glutathione. Metabolism and Function ", ed. by I. M. Arias and W. B. Jacoby, Ravan Press, New York, 1976, pp. 77-114.
2. E. Boyland and L. F. Chasseaud, Adv. Enzymol., 1973, **32**, 173; L. F. Chasseaud, Adv. Cancer Res., 1979, **29**, 175.
3. S. B. Haber, USP 4590205 (Chem. Abs., 1984, **100**, 22571).
4. S. Nakamura, M. Kondo, and Y. Tsuda, 114th Annual Meeting of the Pharmaceutical Society of Chemistry of Japan, Tokyo, March, 1994, Abstracts of Papers 2, p. 275.
5. J. N. M. Commandeur, F. J. J. DeKanter, and N. P. E. Vermeulen, Mol. Pharmacol., 1989, **36**, 654; J. N. M. Commandeur, G. J. Stijntjes, J. Wijngaard, and N. P. E. Vermeulen, Biochem. Pharmacol., 1991, **42**, 31.
6. (a) L. D. Arnold, T. H. Kalantar, and J. C. Vederas, J. Am. Chem. Soc., 1985, **107**, 7105. (b) G. A. Flynn and R. J. Ash, Biochem. Biophys. Res. Communs., 1990, **166**, 673. (c) R. P. Hanzlik, P. E. Weller, J. Desai, J. Zheng, L. R. Hall, and D. E. Slaughter, J. Org. Chem., 1990, **55**, 2736. (d) R. J. S. Hickman, B. J. Christie, R. W. Guy, and T. J. White, Aust. J. Chem., 1985, **38**, 899.
7. P. Garner and J. M. Park, J. Org. Chem., 1987, **52**, 2361.
8. D. L. Hughes, Org. React., 1992, **42**, 335.
9. I. Nakagawa and T. Hata, Tetrahedron Lett., 1975, 1409.
10. S. C. Cherkofsky, EP 24042 (Chem. Abs., 1981, **95**, 42893).
11. Attempted coupling of 5-bromo-3-(*p*-methanesulfonylphenyl)-2-(*p*-fluorophenyl)-thiophene with Ac-L-Cys-OMe in the presence of CuI in DMF[6d] resulted in the formation of **12** with 70 %ee in 35-43 % yield.
12. All new compounds described herein gave satisfactory analytical and spectral data consistent with the assigned structures.
13. Determined by hplc with a CHIRALPAK® AD column (0.46 ϕ x 25 cm), DAICEL Chem. Ind., Ltd.

Received, 13th February, 1995