Tetrahedron Letters, Vol.32, No 29, pp 3529-3530, 1991
Printed in Great Britain

0040-4039/91 $3.00 + 0
Pergamon Press plc

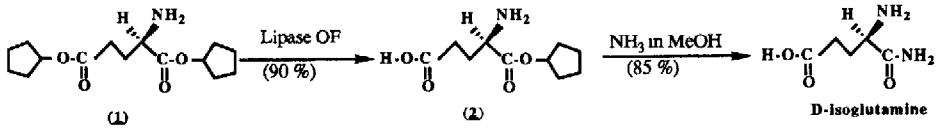
# THE SYNTHESIS of D-ISOGLUTAMINE by A CHEMOENZYMATIC METHOD

Shih-Hsiung Wu*[a], Fei-Ya Chu[b], Chung-Ho Chang[a] and Kung-Tsung Wang[ab]

[a]Institute of Biological Chemistry, Academia Sinica,
and
[b]Department of Chemistry, National Taiwan University,
Taipei, Taiwan, ROC

Summary : α-Cyclopentyl D-glutamate was obtained from dicyclopentyl D-glutamate utilizing lipase-catalyzed hydrolysis. The monoester was then treated with $NH_3$ in methanol to produce D-isoglutamine.

D-Isoglutamine is a component of peptidoglycans in the bacterial cell wall, which is necessary for immunoadjuvant activity[1]. The synthesis of D-isoglutamine has been achieved starting with D-glutamic acid by chemical methods[2]. Here, as shown below, a novel and facile way to synthesize D-isoglutamine by a chemoenzymatic method is developed.




(1) (2)

First, dicyclopentyl D-glutamate (1) is regioselectively hydrolyzed by Candida lipase to obtain the α-cyclopentyl D-glutamate (2), and then treated with ammonia in methanol solution to produce D-isoglutamine. The key features of the present method focus on the regioselectivity of enzymatic hydrolysis of D-glutamate diesters. In previous reports, dimethyl aminoglutarate whose structure is similar to glutamate has been hydrolyzed enantiotopically and regioselectively by pig liver esterase (PLE) to afford the R-monoester and by adding the benzyloxycarbonyl group to amino moiety, PLE could reverse its selectivity and produce the S-monoester. Both chiral monoesters were applied to synthesize (S)- or (R)-ß-lactam compounds and (+)-negamycin.[3] Proteases such as subtilisin and chymotrypsin have been used to prepare the γ-cycloalkyl L-glutamate and ß-cycloalkyl L-aspartate by the regioselective hydrolysis of the dicycloalkyl esters.[4] Owing to the slow reaction toward D-

amino acid derivatives, proteases are not good catalysts to hydrolyze D-glutamate diesters. After screening, only the lipase from Candida cylindracea which has been widely used in the kinetic resolution of alcohols and acids[5] can hydrolyze glutamic acid diesters. Moreover, the alcohol moieties of glutamic acid diesters can greatly influence the regioselectivity of the lipase. As shown in Table 1., dicyclopentyl D-glutamate showed higher α/γ selectivity than other diesters examined.

Table I. Regioselectivity of the lipase from Candida cylindracea on D-glutamate diesters substrates with different alcohol moieties.

| | ratios (α/γ) of glutamic acid α- and γ-monoester produced by lipase-catalyzed hydrolysis[a] |
|---|---|
| dibutyl | 0.8 |
| dibenzyl | 1.6 |
| dicyclopentyl | 20 |
| dicyclohexyl | 5.1 |

[a]To a solution of 1 g of the diester in 30 mL of phosphate buffer (pH 7.0, 0.1 M) was added 20 mg of lipase OF (crude powder, Meito Sangyo Co., Ltd, Japan) and stirred at room temp. The ratios of D-Glu α- and γ-monoesters could be measured by amino acid analyzer.

In short, enzymes used in the right step would make the synthesis of organic compounds much easier.

Acknowledgement : This work was supported by National Science Council, Taiwan, ROC.

REFERENCES :

1. F. Ellouz, A. Adam, R. Ciorbaru, and E. Lederer, Biochem. Biophys. Res. Commun., 59 (1974) 1317.

2. R. Straka, and M. Zaoral, Collect. Czech. Chem. Commun., 42 (1977) 560.

3. (a) M. Ohno, S. Kobayashi, T. Iimori, Y. F. Wong, and T. Izawa, J. Am. Chem. Soc. 103 (1981) 2405. (b) Y. F. Wong, T. Izawa, S. Kobayshi, and M. Ohno, J. Am. CHem. Soc. 104 (1982) 6465.

4. (a) S. H. Wu, L. C. Lo, S. T. Chen, and K. T. Wang, J. Org. Chem. 54 (1989) 4220. (b) L. C. Lo, S. H. Wu, and S. T. Chen, J. Chin. Chem. Soc. 36 (1989) 459.

5. C. J. Sih, and S. H. Wu, Top. Stereochem. 19 (1989) 63 and references cited therein.

(Received in Japan 12 February 1991)