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DIVERSIFIED SYNTHETIC APPROACHES TO THE CARBAPENEM ANTIBIOTICS BASED ON SYMMETRIZATION-ASYMMETRIZATION CONCEPT[1]

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Abstract: cis-Fused bicyclic β-lactam compound **9**, a key intermediate to cis-substituted carbapenem antibiotics, has been synthesized in optically pure form based on symmetrization-asymmetrization concept.

We have shown that the enantioselective total synthesis of some useful antibiotics can be efficiently achieved by reasonable combination of enzymatic and non-enzymatic procedures[2]. The synthetic strategy for such optically active natural products is designed by the following principle.

(1) Symmetrization: retrosynthesis is performed to generate, from the target molecule, a simplified symmetric diester in the prochiral or meso form.

(2) Asymmetrization: the symmetric diester is subjected to asymmetric hydrolysis with pig liver esterase (PLE) to generate the corresponding chiral half-ester (enzymatic conversion of a σ-symmetry substrate to a C_1-symmetry intermediate[3])

(3) Non-enzymatic procedures: the chiral half-ester is converted to the target molecule and related molecules by means of usual organic synthesis.

We already published our first enantioselective synthesis of the various types of carbapenem antibiotics[4] according to the concept (**3→2→1**) (Scheme 1), and wish to report here two new synthetic approaches to carbapenem antibiotics (**5→4→1**, and **7→6→1**). A bicyclic β-lactam compound **9** was generated as an intermediate from the symmetrization-retrosynthesis of **1** and the optically active half-ester **4** has been shown already to be formed by enzyme-mediated hydrolysis of symmetric diester **5** in excellent chemical (98%) and optical (96% ee) yields[5]. Thus, methyl cis-amino-carboxylate **8a**, mp 50-51°C, $[\alpha]_D^{25}$+21.33 (c 1.00, $CHCl_3$), (R^1=Me, R^2=CBZ)

obtained from **4** by conventional procedures[5] (91% yield), was treated with 0.25N-NaOH in acetone to afford an amino acid (**8b**, R^1=H, R^2=CBZ), mp 143-144°C, in quantitative yield. The CBZ group was removed easily with 30% HBr-AcOH and the resulted salt (HBr) of the amino acid was neutralized with Amberlite IR-120B to afford the free amino acid **8c**, (R^1=R^2=H), mp. 170-172°C, $[\alpha]_D^{22}$+26.8°(c 1.0, H_2O). The β-amino acid **8c** was now cyclized to the corresponding bicyclic β-lactam compound **9**, mp 139-140°C, $[\alpha]_D^{22}$-13.0°(c 0.50, $CHCl_3$), with our condensing system[6], Ph_3P-$(PyS)_2$/CH_3CN in 70% yield. The successful conversion of **5** to the optically pure compound **9** with the desired absolute configuration constitutes a formal enantioselective synthesis of carbapenem antibiotics, since the racemic compound[7] **9** prepared from 1,4-cyclohexadiene and N-chlorosulfonylisocyanate was already converted to racemic cis-carbapenem. Next, the third approach to the carbapenem antibiotics (**7**→**6**→**1**) was investigated. A meso diester **7** containing pyrrolidine ring moiety was generated as the starting material from the symmetrization-retrosynthesis. Thus, the diester **7** was prepared according to the method by Cignarella and Nathansohn[9], and treated with PLE under our standard conditions [**7** (350 mg), PLE (621 units), 0.05M phosphate buffer solution (31.5 ml), acetone (3.5 ml), 30°C, 8h] to afford the chiral half-ester **6** in 85% yield. The optical purity was determined to be 80% ee by NMR shift reagent[10] after converting to the t-butyl ester. The absolute configuration of the half-ester **6** was determined to be as shown in Scheme 3 by converting to the known (R)-1-benzylhomoproline methyl ester[11] **12** after selective elongation of the methylester of **10**. However, it was found that the bicyclic β-lactam formation from such five-membered ring system was miserable in yields. Therefore, the third approach was considered to be impractical.

Among the three approaches to carbapenem antibiotics developed so far, the total elegancy of the synthesis may be dependent upon the availability of the symmetric diesters, optical purity of the chiral half-esters obtained by the enzyme-catalyzed hydrolysis, and the efficiency of the conversion to the target molecules from the half-esters and the first (**3**→**2**→**1**) and second (**5**→**4**→**1**) routes are considered more efficient. An important feature of the symmetrization-asymmetrization concept is able to design symmetric substrates in multiple forms from one target molecule and able to make choice of them according to the purpose of the synthesis.

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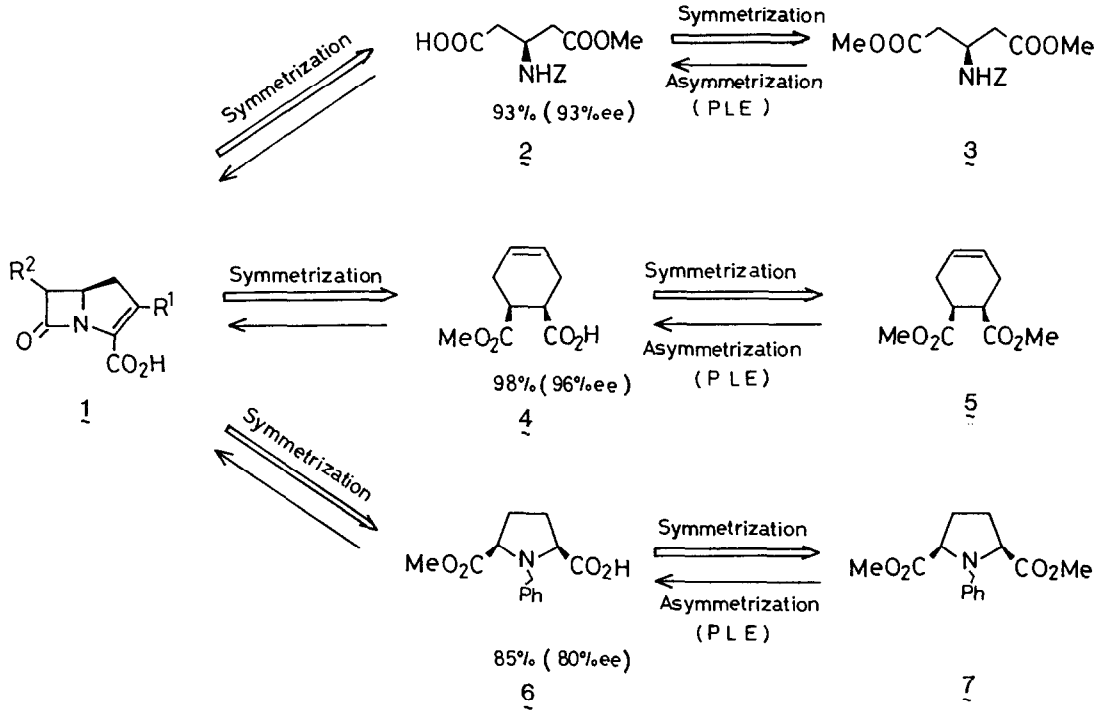
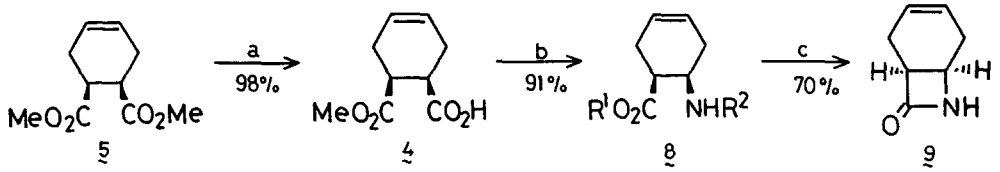
Scheme 1 **Symmetrization–asymmetrization Concept**



Scheme 2

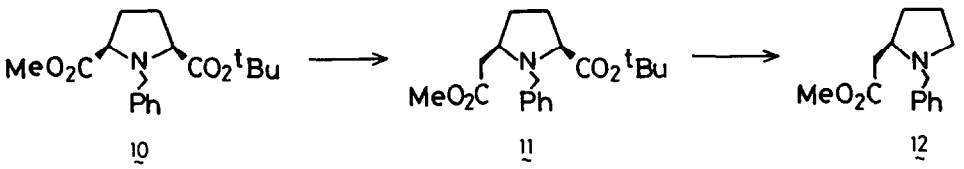


a) PLE / pH8.0 phosphate buffer - 10%acetone , 30°C , 3h

b) (1) $ClCO_2Et$-Et_3N (2) NaN_3 (3) Δ (4) $PhCH_2OH$ - p-TsOH (5) NaOH (6) HBr - AcOH

C) Ph_3P - PySSPy / CH_3CN

Scheme 3



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