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A GENERAL APPROACH TO TRANS-CARBAPENEM ANTIBIOTICS. ENANTIOSELECTIVE SYNTHESIS OF KEY INTERMEDIATES FOR (+)-PS-5, (+)-PS-6, and (+)-THIENAMYCIN

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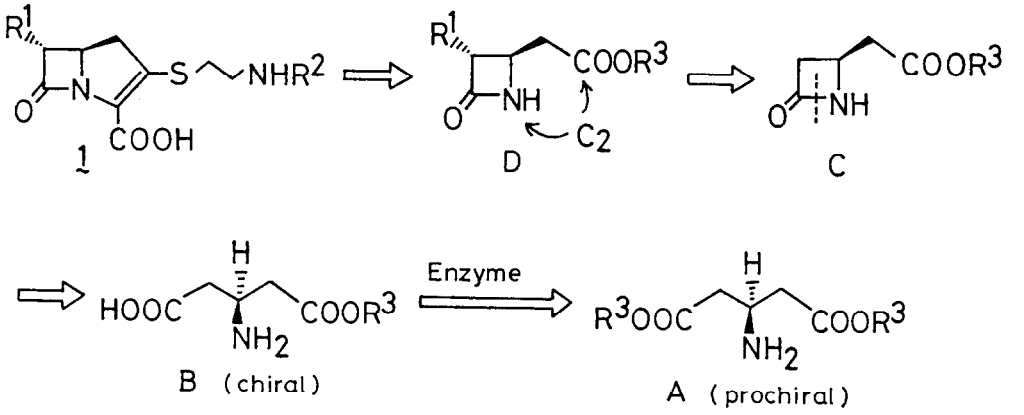
Summary: (S)-4-[(Methoxycarbonyl)methyl]-2-azetidinone prepared by chemico-enzymatic approach has been efficiently converted to key intermediates for the synthesis of natural trans-carbapenem antibiotics, (+)-PS-5, (+)-PS-6, and (+)-thienamycin.

The control of absolute stereochemistry is indeed a central problem in the synthesis of biologically significant enantiomers of natural products. An efficient access to chirality is the enantioselective generation of an asymmetric center from a prochiral starting material by introduction of an enzymatic step. We wish to report here a general approach to the enantioselective synthesis of trans-carbapenem antibiotics, (+)-PS-5, (+)-PS-6 and (+)-thienamycin, through (S)-3-amino-4-methoxycarbonylbutyric acid enzymatically generated. As shown in the general strategy of Scheme I, we noticed that the synthetic problem for the carbapenem antibiotics[1] can be extremely simplified by considering a symmetric factor within the carbapenem nucleus, and have already demonstrated that the prochiral (symmetric) dimethyl 3-benzyloxy-

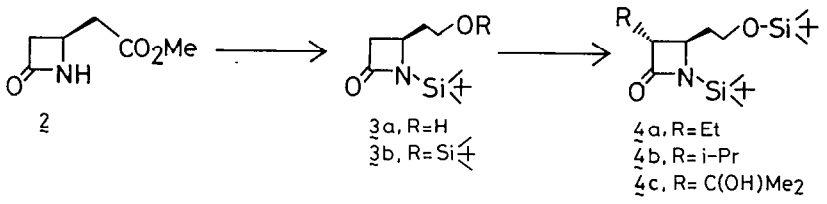
Scheme I

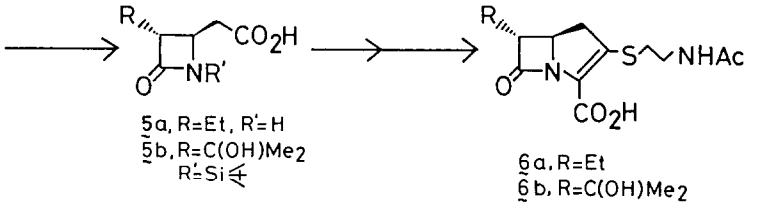


carbonylaminoglutarate (A, R=Me) was asymmetrically hydrolyzed with pig liver esterase and the resulted chiral half-ester B was cyclized to β-lactam C with Ph_3P-PySSPy-CH_3CN system[2,3]. The chiral half-ester B (R=Me) is now easily available in quantity by use of the enzymes of microbial origin[4] (quantitative yield and 98% ee before recrystallization) and the chiral β-lactam C (R=Me) was more efficiently prepared in a large scale by improved procedures[3,4](about 90% yield). Thus, (S)-4-[(methoxycarbonyl)methyl]-2-azetidinone(2) was subjected to reduction with $LiAlH_4$ in THF after protection with t-Bu(Me)$_2$SiCl and Et_3N in DMF (0°C, 1h→25°C, 15min) to afford 4-hydroxyethyl derivative 3a [$[\alpha]_D^{25}$ -52.90 (c 1.98, $CHCl_3$)]. The hydroxyl group of 3a was further protected by silylation with t-Bu(Me)$_2$SiCl and Et_3N to afford 3b, [$[\alpha]_D^{25}$-49.24 (c 1.98, $CHCl_3$)], in 97% overall yields from 2. The protected β-lactam 3b was also obtained by reduction of 2 with $NaBH_4$-LiCl in DME followed by simultaneous silylation (72% overall yields from 2). Stereocontrolled introduction of ethyl, isopropyl and acetyl groups at the 3-position of 2-azetidinone 3b was achieved through the enolate anion (C→D). Addition of ethyl iodide (3.7eq) (-20°C, 3h) to a THF solution containing enolate anion of 3b generated with LDA (1.2eq) and HMPA (1.9eq) afforded thermodynamically favored trans-β-lactam 4 in 92% yield after column chromatography on SiO_2 [hexane:ether=5:1; 4a, $[\alpha]_D^{25}$-39.59° (c 2.92, $CHCl_3$)]. Selective removal of the protective group of the hydroxyl function with N-HCl in MeOH (25°C, 1h) followed by Jones oxidation and removal of the N-silyl group with N-HCl in MeOH (25°C, 4h) afforded 5a in 50% yield after column chromatography on SiO_2 [$CHCl_3$:CH_3COCH_3=3:1; 5a, $[\alpha]_D^{25}$+48.98° (c 1.14, $CHCl_3$)]. Incorporation of i-propyl group also occurred in a stereocontrolled manner by the similar reaction of 3b and i-PrI to afford 4b in 86% yield, $[\alpha]_D^{20}$ -67.53° (c 2.29, $CHCl_3$). Aldol condensation of 3b with acetaldehyde (LDA in THF, -78°C) afforded a mixture of the expected aldol products in a nonstereoselective manner, but aldol condensation of 3b with acetone under the same condition afforded exclusively trans-β-lactam 4c in 96% yield, $[\alpha]_D^{25}$-35.63° (c 1.0, $CHCl_3$). Treatment of 4c with N-HCl in MeOH (0°C, 30min) followed by oxidation with Collin's reagent afforded 5b in 80% yield. Conversion of 2 to 5a constitutes a formal enantioselective synthesis of (+)-PS-5 (1; R^1=Et, R^2=Ac), since 5a was already converted to PS-5[5]. The compound 4b is a key intermediate for the synthesis of (+)-PS-6[5a] (1, R^1=i-Pr, R^2=Ac) and 5b was efficiently converted to a epicarpetimycin homologue 6b by employing Merck method[1b,6] (Scheme II). Next, the two-step acylation-reduction sequence originally developed by Saltzmann et al[7] was studied for the stereocontrolled introduction of the hydroxyethyl side chain of 1. Direct acylation of 3b with N-acetylimidazole (2.3eq) (2.3eq of LDA, THF, -78°C, 20min→quenched with NH_4Cl at -78°C) also provided only trans acetyl derivative 7 in 81% yield, $[\alpha]_D^{20}$-24.43° (c 0.87, $CHCl_3$). Stereoselective reduction of 7 was satisfactorily achieved by treatment of 7 with K-selectride (2.6eq) in Et_2O[7b] to afford 8 in 98% yield on the basis of recovered 7. The 8R/8S (carbapenem numbering) or erythro/threo product ratio of 8 was found to be 10 to 1 on the basis of ^{1}H-NMR analysis, and 8 was an

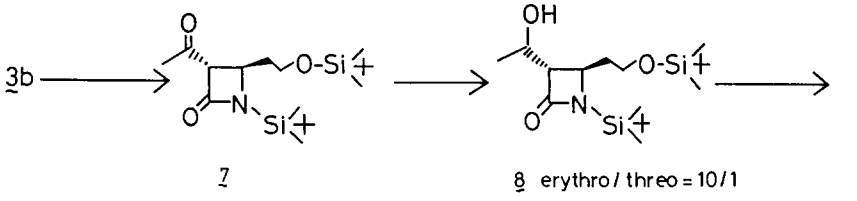
inseparable mixture by tlc. However, the mixture was cleanly separated at the next step. The hydroxyl group of 8 was protected with p-nitrobenzyl chloroformate (PNBOCOCl) in the presence of DMAP, and the resulted mixture was subjected to column chromatography on SiO_2 (hexane: Et_2O=1:1) affording the desired erythro product 9 in 71% yield [R_f=0.14, $[\alpha]_D^{20}$-5.66°(c 1.08, $CHCl_3$)] and the threo isomer in 7% yield [R_f=0.21, $[\alpha]_D^{20}$-19.43 (c 1.97, $CHCl_3$)]. Removal of the silyl groups of 9 (2N-HCl, THF, 25°C, 12h) afforded 10 quantitatively, a known intermediate to 1, $[\alpha]_D^{20}$+0.85 (c 1.97, $CHCl_3$). Therefore, conversion of 2 to 10 constitutes a formal enantioselective synthesis of (+)-thienamycin. The key features of the present methodology includes the following: (1) the monocyclic β-lactam 2 prepared by chemicoenzymatic procedure is indeed a versatile intermediate for various trans-carbapenem antibiotics in natural form; (2) the general approach to carbapenem antibiotics developed here is characterized by remarkable simplicity and efficiency.[9,10,11]

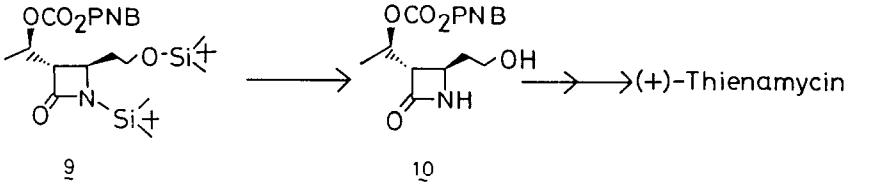
Scheme II





Scheme III





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5. (a) Kametani, T.; Honda, T.; Nakayama, A.; Sasakai, Y.; Mochizuki, T.; Fukumoto, K.; J. Chem. Soc. Perkin I, 1981, 2228. (b) Favara, D.; Omodei-Sali, A.; Consonni, P.; Depaoli, A. Tetrahedron Lett. 1982, 23, 3105.
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9. Further investigation of the present approach to carbapenem antibiotics is now in progress in our laboratory and the results will be reported in due course.
10. All materials described here gave MS, IR, and NMR spectra consistent with their structures.
11. For recent synthesis of 1 using chiral templates, see (a) Ikota, N.; Yoshino, O.; Koga, K. Chem. Pharm. Bull. 1982, 30, 1929, (b) Chida, N.; Miyashita, M.; Yoshikoshi, A.; 25th Symposium on the Chemistry of Natural Products, Tokyo, Abstracts, p. 108 (1982).

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