분류번호	S-2

제 목	SYNTHETIC DEVELOPMENT OF NEW 1β-SUBSTITUTED CARBAPENEMS
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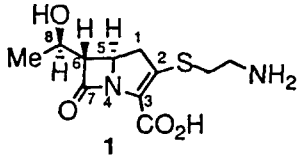
The Development of new asymmetric induction methods useful for syntheses of biologically active natural products and drugs, using C4-chiral 1,3-thiazolidine-2-thiones, has been a recent focus of interest.[1-8] The present account describes the significance of particular heterocycles in the synthetic development of new 1β-substituted carbapenems.

A fungal metabolite, (+)-thienamycin (1) has attracted one's attention as a hopeful candidate for new-generation antibiotic drugs because of its strong antimicrobial activities and wide antimicrobial spectra due to the extensive inhibition against various β-lactamases. However, it has been serious problems toward a practically useful drug that (+)-thienamycin is fairly labile in the solution and can be metabolized by renal dehydropeptidase-I (DHP-I). Recently, a Merck Sharp & Dohme research group exploited a non-natural β-lactam, imipenem (2), which has been appeared in the drug market as the first carbapenem-type antibiotic drug.[9] However, 2 must be used with a DHP-I inhibitor, cilastatin sodium (3).[9] Thus, a 1β-methylcarbapenem derivative 4 has been disclosed by the same group.[10] It seems to be more hopeful candidate as a new-generation antibiotic because it can directly resist against metabolism by the renal DHP-I without an enzyme inhibitor 3.[10]



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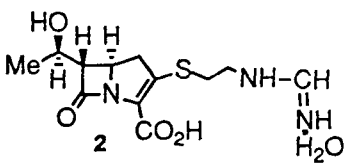

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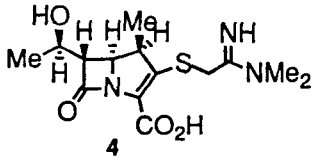

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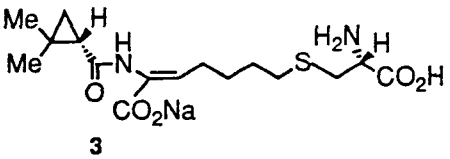

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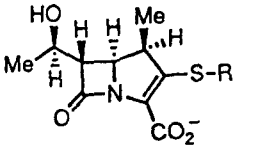
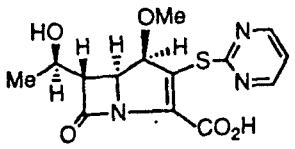
Since discovery of 4, there had been no report on a highly stereoselective introduction method of a methyl group at the 1β-position of the carbapenem before the first paper by us in 1986.[2] Extensive research in our collaboration led to the development of the highly diastereoselective synthesis 1β-substituted carbapenems by utilizing C4-chiral 1,3-thiazolidine-2-thiones.[2] On the basis of our synthetic method, asymmetric syntheses of several new non-natural carbapenems[5,6,8] 5-9 and thienamycin like γ-lactams[7] 10 and 11 were successfully achieved. Synthesis of a carbapenem pendant 12, featuring σ-symmetric heterocycles based on the electron-transfer concept, has been achieved.





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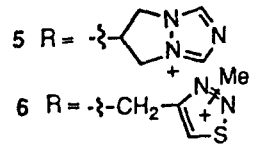

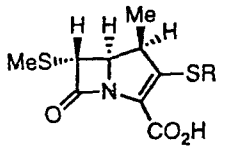

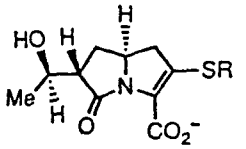

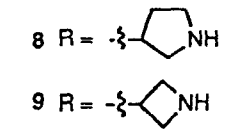

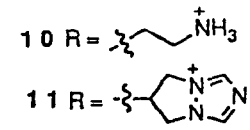

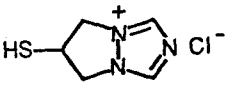

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