SYNTHESIS OF CARBAPENEM-TYPE ANTIBIOTICS

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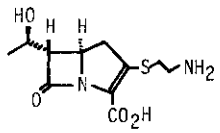
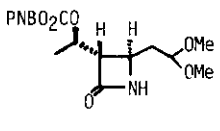
Synthesis of thienamycin (1) and other carbapenem antibiotics by several routes was examined.

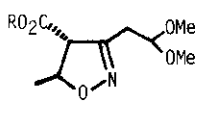
Total synthesis of thienamycin was successfully accomplished from 8R*-trans-azetidinone (2), which was prepared from the isoxazoline (3) by an improved method. The acid obtained from 2 by Jones oxidation was converted to imidazolide, which was treated in situ with the magnesium salt of the mono-p-nitrobenzyl malonate to afford the ketoester (4). The diazo compound (5) was then synthesised by a diazo exchange reaction with tosyl azide in acetonitrile. Thermal cyclization of 5 in the presence of $Rh_2(OAc)_4$ in benzene gave the bicyclic ketoester (6), quantitatively. Introduction of the cysteaminyl moiety to 6 was achieved by adoption of the Merck method to afford the tris-protected thienamycin, the conversion of which to thienamycin (1) has already been reported by the Merck group. Thus, the total synthesis of thienamycin was efficiently achieved.



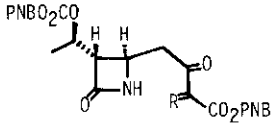
(1)



(2)

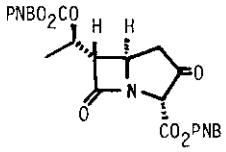


(3)

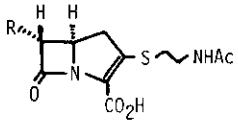


(4) R=H_2

(5) R=N_2



(6)



(7)

Furthermore, introduction of functionalised carbon units to the C_4-position of 4-acetoxy-2-azetidinone derivatives was easily carried out by treatment with corresponding carbanions. The application of this reaction for the synthesis of the PS-series of carbapenem-type antibiotics (7) provided a useful synthetic pathway.