A CHIRAL SYNTHESIS OF CARBAPENEM ANTIBIOTICS FROM PENICILLINS

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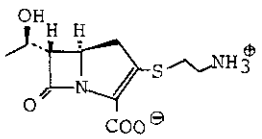
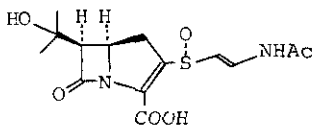
A chiral synthetic method for carbapenem antibiotics from penicillin 3 will be described. A key feature in this synthetic approach is that the amino group in 3 serves as a controlling handle for the stereoselective introduction of two alkyl groups into the C_3- and C_4- positions of the azetidinone rings (4 → 5 and 8 → 9).

The allylazetidinone 5, obtained stereospecifically by a $AgBF_4$-catalyzed reaction of the chloride 4 with allyltrimethylsilane (M. Aratani, K. Sawada and M. Hashimoto, Tetrahedron Lett., 23, 3921 (1982)), was converted to 6. Aldol reaction and alkylation of the dianion derived from 6 with electrophiles gave stereo- and chemo-selectively the trans-alkylated products 7, one of which was converted into the known intermediate 10 for the synthesis of (+)-thienamycin 1.

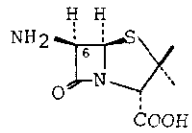
To synthesize the cis-substituted carpetimycin 2, 5 was transformed into the bicyclic isonitrile 8. Aldol reaction of 8 with acetone followed by stereoselective triphenyltin hydride reduction of the isonitrile group gave 9. The acid 11 derived from 9 was converted to carpetimycin 2 analogs.



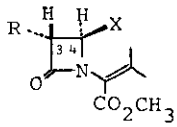
1 thienamycin

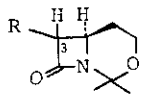


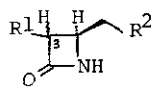
2 carpetimycin A



3







4 : R=Ft, X=Cl
5 : R=Ft, X=$CH_2CH=CH_2$
6 : R=H , X=$CH_2CH=CH_2$
7 : R=Me,Et,MeCH(OH)-,$Me_2C(OH)$-
X=$CH_2CH=CH_2$

8 : R=CN
9 : R=$Me_2C(OH)$-,3α-H

10 : R^1=MeCH(OZ)-,3β-H
R^2= -$CH(OMe)_3$
11 : R^1=$Me_2C(OZ)$-,3α-H
R^2= -COOH