SYNTHESIS OF THIENAMYCIN AND RELATED COMPOUNDS

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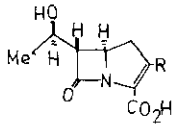
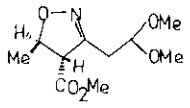
The stereoselective synthesis of an important key intermediate for the synthesis of (±)-thienamycin (1) and an efficient synthetic method for the synthesis of descysteaminylthienamycin (2) derivatives have been developed as follows. By 1,3-dipolar cycloaddition, the nitrile oxide, derived from 3-nitropropanal dimethyl acetal, was added to methyl crotonate to give regio- and stereoselectively trans-4-methoxycarbonyl-3-(2',2'-dimethoxyethyl)-5-methylisoxazoline (3). Reduction of 3 in the presence of hydrogen (5∿6 atm) and Adams catalyst in acetic acid yielded quantitatively a stereoisomeric mixture of the amino alcohol (4). Hydrolysis of 4 followed by treatment with dicyclohexylcarbodiimide gave mainly two trans-azetidinones (5 and 6) together with a small amount of the cis-isomer. On the other hand, reaction of 4 with methylmagnesium iodide yielded the desired trans-azetidinone (5) along with a trace of the cis-one. The stereochemistry of one (6) of the trans-isomers was confirmed by X-ray analysis of a derivative. The trans-azetidinones (5 and 6) were protected with the p-nitrobenzyloxycarbonyl group and then converted to the alcohols and to the thioacetals. One of these thioacetals has already been correlated to thienamycin by a Merck research group.

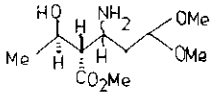
Synthesis of descysteaminylthienamycin derivatives was accomplished using 8S*-trans-azetidinone (6). Protection of 6 with the o-nitrobenzyloxycarbonyl group followed by condensation with o-nitrobenzyl glyoxalate ethylhemiacetal, yielded the alcohol. On reaction with thionyl chloride and 2,6-lutidine, the alcohol gave the unstable chloro compound, which without purification was converted to the phosphorane. Deacetalization using p-toluenesulfonic acid in acetone, followed by neutralization, caused spontaneous intramolecular Wittig reaction to give (±)-8S*-descysteaminylthienamycin protected with o-nitrobenzyl groups.



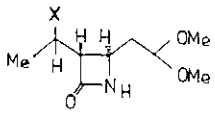
(1) R=$SCH_2CH_2NH_2$
(2) R=H



(3)



(4)



(5) X = OH (R*)
(6) X = OH (S*)