

SYNTHESIS OF THIENAMYCIN AND RELATED COMPOUNDS

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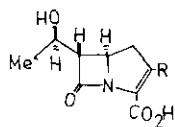
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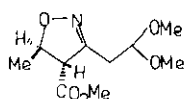
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The stereoselective synthesis of an important key intermediate for the synthesis of (\pm)-thienamycin (**1**) and an efficient synthetic method for the synthesis of descysteamylthienamycin (**2**) derivatives have been developed as follows. By 1,3-dipolar 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.

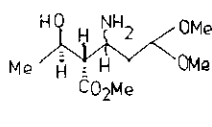
Synthesis of descysteamylthienamycin derivatives was accomplished using 8S⁺-trans-azetidinone (**6**). Protection of **6** with the o-nitrobenzyloxycarbonyl group followed by condensation with o-nitrobenzyl glyoxalate ethylhemiacetal, yielded the alcohol. On reaction with thionyl chloride and 2,6-lutidine, 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 (\pm)-8S⁺-descysteamylthienamycin protected with o-nitrobenzyl groups.

(1) R = -SCH₂CH₂NH₂

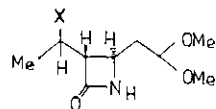
(2) R = H



(3)



(4)



(5) X = OH (R*)

(6) X = OH (S*)