SYNTHETIC STUDIES ON CARBAPENEM ANTIBIOTICS : SYNTHESIS OF 6-PHENOXYACETYLOXY-1-CARBAPEN-2-EM o-NITROBENZYL ESTER

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Abstract —— 6-Phenoxyacetyloxy-1-carbapen-2-em o-nitrobenzyl ester (11) was synthesized from the readily available azetidinone (1), efficiently.

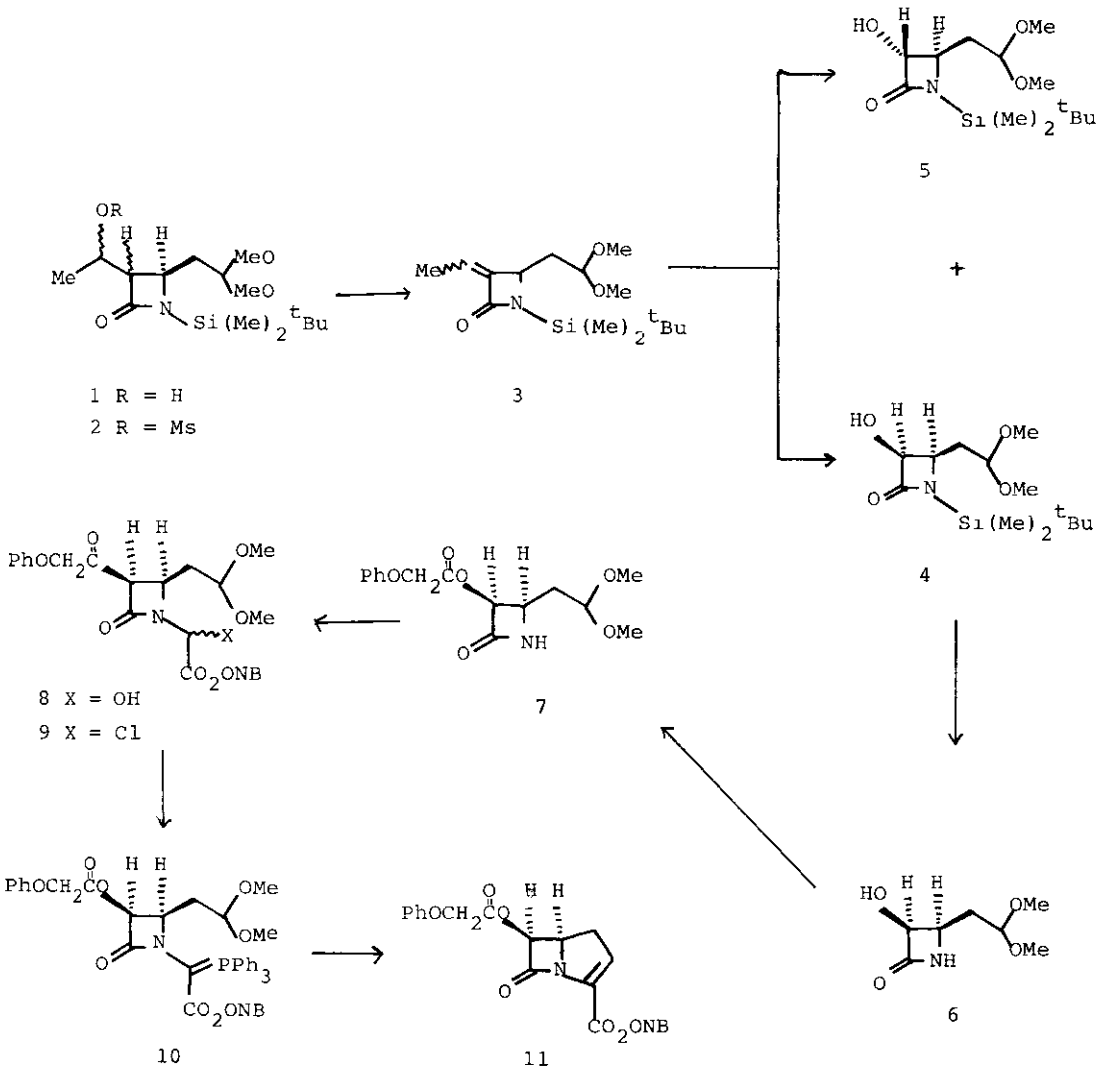
Since the discovery of non-classical β-lactam antibiotics, such as thienamycin[1] and PS-5[2], much attention has been focused on the synthesis of the ring system of 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid. We have already reported the efficient methods, which led us to the synthesis of thienamycin[3] and PS-5[4], for the construction of such carbapenem ring system.

In continuation of our work on the synthesis of carbapenem antibiotics, we have been interested in the synthesis of their derivatives which bear various types of functional groups at the C_6 position, because such replacement of functional groups at that position would be of biological interest. Thus, we have investigated the synthesis of 6-oxygenated carbapenems with the stereochemistry of a cis-relationship between C_5 and C_6 positions.

The readily available azetidinone (1)[3] was converted to its mesylate (2) by treatment with mesyl chloride and triethylamine in methylene chloride. Treatment of 2 with sodium hydride in tetrahydrofuran furnished the olefin (3) as a mixture of E and Z-isomers in good yield. Ozonolysis of 3, followed by sodium borohydride reduction of the ozonide, afforded the alcohols (4 and 5) in a ratio of 7 : 1 in 56 % yield. This fact indicated that the hydride attack occurred from the less hindered α-side to give the β-alcohol (4) predominantly as expected. The major alcohol (4) was then desilylated with tetra-n-butylammonium fluoride in tetrahydrofuran to afford the azetidinone (6) in 94 % yield, whose acylation with phenoxyacetyl chloride in the presence of N,N-dimethylaminopyridine in methylene chloride gave rise to the

ester (7) in 92 % yield. The phosphorane (10) was then prepared from 7 by adoption of Woodward's procedure[5], via the alcohol (8) and the chloride (9), in 67 % yield. Although difficulties were initially encounted in the conversion of the acetal (10) to the carbapenem (11), e.g., attempted deacetalization by treatment with p-toluene-sulfonic acid and perchloric acid in appropriate solvents failed, treatment of 10 with iodotrimethylsilane[6] in methylene chloride, followed by neutralization with sodium hydrogen carbonate afforded the desired carbapenem (11)[7].

Thus, the synthesis of 6-phenoxyacetyloxycarbapenem (11) was achieved and this route would be a useful method for introducing an oxygen function at the C_6-position of a carbapenem ring system.



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7 IR : $\nu_{max.}^{CHCl_3}$ cm^{-1} 1790, 1730 (C=O) and 1342 (NO_2); NMR ($CDCl_3$) δ 3.02 (2H, dd, J = 3.4, 12Hz, C_1-H_2) and 6.52 (1H, t, J = 3.4 Hz, C_2-H). Treatment of 10 with iodotrimethylsilane brought about the partial formation of the hydriodide salt, probably because of the presence of hydriodic acid in the reagent.

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