AN ALTERNATIVE TOTAL SYNTHESIS OF (±)-THIENAMYCIN

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Abstract—— (±)-4β-(2',2'-Dimethoxyethyl)-3α-(1'R*)-p-nitrobenzyloxycarbonyloxyethyl)-2-azetidinone (4) was converted into the thienamycin derivative (2) protected with p-nitobenzyl group, utilizing the carbene insertion reaction and subsequent introduction of the cysteamine moiety developed by the Merck group.

The highly desirable antibiotic activity of thienamycin (1)[1], possessing a novel 1-carbapen-2-em structure, has promoted considerable synthetic efforts which have resulted in its total synthesis.[2-7] We developed an efficient synthesis of β-lactam derivatives, via isoxazolines (3), leading to a formal total synthesis of thienamycin.[6,7] Recently, the Merck research group announced a chiral total synthesis of the antibiotic[3] which involved a novel and useful formation of the [3.2.0]bicyclic ring system by carbene insertion reaction, followed by introduction of the cysteamine moiety.[4] Since our synthetic intermediate (4) has the following advantages; a hydroxyethyl group at the C_3 position with the correct stereochemical arrangement, and a 2',2'-dimethoxyethyl group at the C_4 position which is readily convertible, via the aldehyde, to the carboxylic acid group, we undertook its conversion to the p-nitrobenzyl-protected thienamycin derivative (2)[2] employing the Merck method. Thus we wish to report here an alternative total synthesis of thienamycin which was carried out along these lines.

Hydrolysis of 4[6] with hot aqueous acetic acid, followed by Jones oxidation of the resulting aldehyde at 0°C quantitatively gave the acid (5). After treatment of 5 with N,N'-carbonyldiimidazole, the imidazolide formed was reacted with the magnesium salt[8] of the mono-p-nitrobenzyl ester of malonic acid[3] to afford the β-keto ester (6), ν_{max} ($CHCl_3$) 3420 (NH), 1765, 1750, 1720 cm^{-1} (C=O); δ ($CDCl_3$) 1.42 (3H, d,

J = 6.5 Hz, C_1,-Me), 3.57 (2H, s, $COCH_2CO_2$). The carbene precursor (7), ν_{max} ($CHCl_3$) 2130 cm^{-1} was prepared from 6 in 96 % yield by diazo exchange with p-toluenesulfonyl azide in the presence of triethylamine in acetonitrile at 0°C to room temperature. Decomposition of the diazo ketoester (7) was carried out by refluxing in benzene in the presence of a catalytic amount of rhodium acetate, leading to a quantitative formation of the carbapenam (8), ν_{max} ($CHCl_3$) 1770 and 1748 cm^{-1} (CO); δ ($CDCl_3$) 1.52 (3H, d, J = 6.5 Hz, C_1,-Me), 4.77 (1H, s, C_3-H). On treatment of 8 with diphenyl chlorophosphate in the presence of one mole equivalent of diisopropylethylamine and a catalytic amount of 4-dimethylaminopyridine in acetonitrile[3] at 0°C, followed by addition of diisopropylethylamine and N-(p-nitrobenzyloxycarbonyl)-cysteamine[2] and stirring overnight at -15°C, the protected thienamycin derivative (2)[2] was obtained in 70 % yield. The synthetic product (2) was identical to an authentic sample by comparison of the ir and nmr spectra and tlc behaviors.

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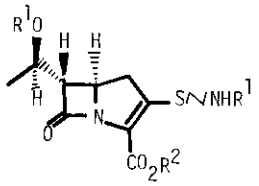
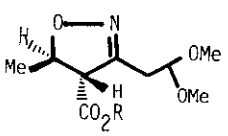


(1) $R^1 = R^2 = H$

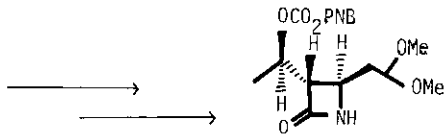
(2) $R^1 = CO_2PNB$, $R^2 = PNB$

PNB = p-Nitrobenzyl

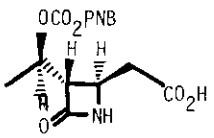


(3)

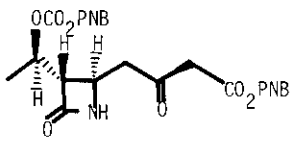
R = Me or ^tBu



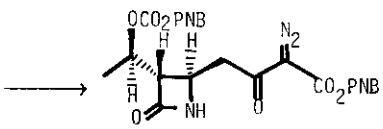
(4)



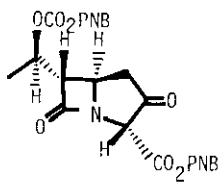
(5)



(6)



(7)



(8)

→ (2)

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