AN ALTERNATIVE TOTAL SYNTHESIS OF (±)-THIENAMYCIN

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Abstract—(±)-4β-(2',2'-Dimethoxyethyl)-3α-(1'R*)-p-nitrobenzylcarbonyloxyethyl)-2-azetidinone (4) was converted into the thienamycin derivative (5) 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), possessing a novel 1-carbapen-2-em structure, has promoted considerable synthetic efforts which have resulted in its total synthesis. We developed an efficient synthesis of β-lactam derivatives, via isoxazolines (3), leading to a formal total synthesis of thienamycin. Recently, the Merck research group announced a chiral total synthesis of the antibiotic 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. Since our synthetic intermediate (4) has the following advantages; a hydroxyethyl group at the C3 position with the correct stereochemical arrangement, and a 2',2'-dimethoxyethyl group at the C4 position which is readily convertible, via the aldehyde, to the carboxylic acid group, we undertook its conversion to the p-nitrobenzyl-protected thienamycin derivative (5) 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 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'-carbonyldimidazole, the imidazolidine formed was reacted with the magnesium salt of the mono-p-nitrobenzyl ester of malonic acid to afford the β-keto ester (6), \( \nu_{\text{max}} \) (CHCl\(_3\)) 3420 (NH), 1765, 1750, 1720 cm\(^{-1}\) (C=O); δ (CDCl\(_3\)) 1.42 (3H, d, J = 6 Hz, CHC\(_2\)).
J = 6.5 Hz, C1,-Me), 3.57 (2H, s, COCH2CO2). The carbene precursor (7), νmax (CHCl3) 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), νmax (CHCl3) 1770 and 1748 cm⁻¹ (CO); δ (CDCl3) 1.52 (3H, d, J = 6.5 Hz, C1,-Me), 4.77 (1H, s, C3-H). On treatment of 8 with diphenyl chlorophosphosphate in the presence of one mole equivalent of diisopropylethylamine and a catalytic amount of 4-dimethylaminopyridine in acetonitrile at 0°C, followed by addition of diisopropylethylamine and N-(p-nitrobenzyloxycarbonyl)-cysteamine and stirring overnight at -15°C, the protected thionamycin derivative (9) was obtained in 70 % yield. The synthetic product (9) 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

$R = \text{Me or } t\text{Bu}$
REFERENCES AND NOTES


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