A FORMAL TOTAL SYNTHESIS OF THIENAMYCIN

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Abstract — Careful hydrolysis of the amino alcohol (3), obtained from trans-4-methoxycarbonyl-3-(2',2'-dimethoxyethyl)-5-methyl-isoxazoline (2), followed by treatment with dicyclohexylcarbodiimide gave two trans-azetidinones (4 and its epimer) together with the cis-isomer (5). Reaction of 3 with methylmagnesium iodide yielded the trans-azetidinone (4) along with the cis-one (5). The trans-azetidinone (4) was converted into the alcohol (7) and the thioacetal (8), which had been correlated to thienamycin (1).

In the preceding papers[1], we reported the preparation of an intermediate for the synthesis of (±)-8S*-thienamycin and an efficient route to (±)-8S*-descysteaminyl-thienamycin starting from the isoxazoline (2). We have further investigated the stereoselective synthesis of thienamycin (1), the potent antibiotic from Steptomyces cattleya[2], and found suitable reaction conditions for achieving this goal which we now wish to report.

Hydrolysis of the stereoisomeric mixture of the amino alcohol (3), which was prepared by catalytic reduction of the isoxazoline (2), was carefully carried out by stirring at room temperature for 6 h with one mole equivalent of sodium hydroxide in aqueous methanol, in contrast to the previous hydrolysis carried out at refluxing temperature[1]. After neutralization with sulfuric acid, the resulting free amino acid was heated for 5 h at 100° C with dicyclohexylcarbodiimide in aqueous dioxane. Silica gel column chromatography of the product afforded two azetidinone fractions. One fraction, obtained in 0.5 % yield from the amino alcohol (3), was established to be the cis-substituted azetidinone (5), and the other, obtained in 22 % yield from 3, was composed of the two trans-azetidinones (4 and its epimer at C_8), which

were not separable by ordinary chromatographical techniques. The hydroxyl group of the latter fraction was protected with the p-nitrobenzyloxycarbonyl group by reaction with the corresponding chloride in the presence of 4-dimethylaminopyridine. Deacetalization of the acetal (6 and its epimer at C_8) followed by reduction with sodium borohydride gave an epimeric mixture of the alcohol (7 and its epimer at C_8). On the other hand, treatment of the acetal (6 and its epimer) with N-p-nitrobenzyloxycarbonylcysteamine in dry trifluoroacetic acid at room temperature gave an epimeric mixture of the thioacetal (8 and its C_8 epimer). The NMR spectra (200 MHz) of both products (7 and epimer, and 8 and epimer) revealed that they were a mixture of $8R^*$-(7 and 8) and $8S^*$-isomers in an approximate ratio of 1 : 2.5.

From the above result and others[3], it was considered that the abominable epimerization occurred during both reactions, the hydrolysis of 3 at high temperature and β-lactam formation using dicyclohexylcarbodiimide. Thus ring closure of the amino alcohol (3) was examined by different methods which excluded both the aforementioned procedures. Reaction of 3 with excess methylmagnesium iodide[4] in a mixture of ether and tetrahydrofuran at room temperature for 16 h yielded the desired trans-azetidinone (4) in moderate yield, together with a trace of the cis-isomer (5) which was identical to the above product formed using dicyclohexylcarbodiimide. The homogenity of this trans-compound (4) was confirmed by its conversion into the alcohol (7) and the thioacetal (8), under the same reaction conditions as described above. Since 7 and 8 had already been transformed to thienamycin (1)[5], the formal total synthesis of the antibiotic was accomplished.

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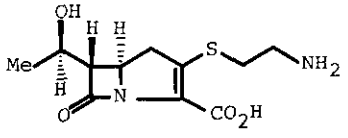

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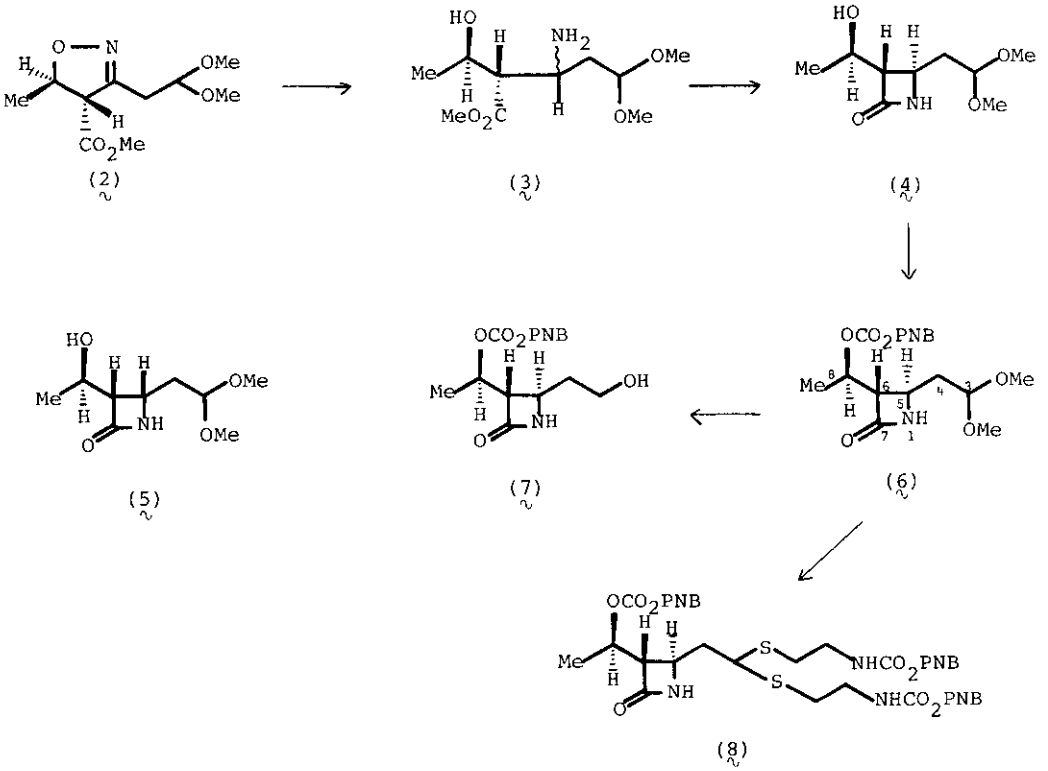

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