SYNTHESIS OF ISTAMYCIN A

Sir:

As reported in a previous paper\(^1\), two new aminoglycoside antibiotics, istamycins A and B were discovered in a culture filtrate of Streptomyces tenjimariensis nov. sp., and their structures were determined. We now wish to report the total synthesis of istamycin A starting from 3',4'-dideoxyneamine. The key step involves an aziridine ring formation\(^2\) for the stereospecific synthesis of the diaminocyclitol moiety, as shown in Scheme 1.

Acylation of 3',4'-dideoxyneamine (1), previously synthesized by UMEZAWA et al.\(^3\,4\), with ethyl chloroformate and sodium carbonate in 70% aqueous methanol overnight at room temperature, followed by column chromatography on Amberlite CG-50 (NH\(_4^+\)) resin using 0.1 N ammonia for the elution, afforded 6'-N-ethoxy-carbonyl-3',4'-dideoxyneamine (2, 21% yield), \([\alpha]_D^2 + 73^\circ\) (c 0.67, H\(_2\)O). The free amino groups of 2 were protected with benzoxycarbonyl group by reaction with benzyl S-4,6-dimethylpyrimid-2-ythiocarbonate in 80% aqueous ethanol overnight at room temperature to yield 1,3,2'-tri-N-benzoxycarbonyl-6'-N-ethoxy-carbonyl-3',4'-dideoxyneamine monohydrate (3, 89% yield), \([\alpha]_D^2 + 35^\circ\) (c 1, CHCl\(_3\)). Treatment of 3 with sodium hydride (50% in mineral oil) in anhydrous N,N-dimethylformamide at room temperature for 5 hours gave the 1,6-carbamate (4, 77% yield), IR (KBr), 1765 cm\(^{-1}\). The 5-hydroxyl group of 4 was protected with tetrahydropyranyl group by reaction with 3,4-dihydro-2H-pyran in anhydrous N,N-dimethylformamide in the presence of p-toluenesulfonic acid overnight at room temperature to afford the 5-O-tetrahydropyranyl derivative (5, 48% yield). The 1,6-cyclic carbamate group of 5 was removed by treatment with 0.05 M barium hydroxide at 60°C for 1.5 hours to give the amino alcohol 6 in 65% yield.
yield. Protection of the 1-amino group in 6 with ethyl chloroformate and sodium carbonate in 67% aqueous methanol followed by mesylation of the 6-hydroxyl group with methanesulfonyl chloride in pyridine overnight at room temperature yielded the 1-N-ethoxycarbonyl-6-O-mesyl derivative (7, 91% yield). Formation of the key intermediate aziridine 8 was achieved by the reaction of 7 with sodium ethylate in anhydrous tetrahydrofuran at -40° to -10°C for 10 hours under argon atmosphere. The following treatment of the compound 8 with sodium benzoate in anhydrous N,N-dimethylformamide at 100°C for 5 hours afforded the new 1,4-diaminocyclitol derivative (9) in 72% yield, [α]D +60° (c 0.4, CHCl3).

Removal of the O-benzoxy group in 9 with 12% ammonia in methanol overnight at room temperature, followed by O-methylation with ethereal diazomethane in a dichloromethane solution in the presence of aluminum chloride at 0°C for an hour gave compound 10 in 40% yield, [α]D +31.5° (c 1, CHCl3), PMR (CDCl3), δ 3.35 (OCH3). Successive removals of O-tetrahydropyran group in 10 by treatment with a mixture of acetic acid, methanol and water (7: 5: 3) at 50°C overnight and of N-benzyl-oxy carbonyl groups by catalytic hydrogenation with 5% palladium on carbon under atmospheric pressure for 2.5 hours gave the di-N-ethoxy carbonyl derivative (11). Compound 11 was reduced by diaborane in tetrahydrofuran at 50°C for 10 hours and thereafter at room temperature for 13 hours to give compound 12 (48% yield), which was purified by column chromatography on Amberlite CG-50 (NH4+) resin using 0.4 N ammonia as eluant and 5% palladium on carbon under atmospheric pressure and found to be identical with deglycylistamycin A (named istamycin A0) in all respects.

Compound 12 was treated with 3.1 equivalents of benzyl S-4,6-dimethylpyrimid-2-ylthiocarbonate in methanol in the presence of triethylamine at room temperature for 3 hours to yield the 1,2',6'-tri-N-benzyloxycarbonyl derivative 13 in 56% yield. Acylation of 13 with the N-hydroxy succinimide ester of N-benzyloxycarbonylglycine in dioxane at 90°C for 2 hours, followed by catalytic hydrogenation with 5% palladium on carbon in a mixture of acetic acid, methanol and water (1: 2: 1) under atmospheric pressure and by column chromatography on Amberlite CG-50 (NH4+) resin using 0.4 N ammonia as eluant, afforded synthetic istamycin A (14), which was isolated as the hemicarbonate (38% yield based on 13) and found to be identical with an authentic sample derived from fermentation13 in all respects including antimicrobial activity.

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