SYNTHESIS OF ISTAMYCIN A

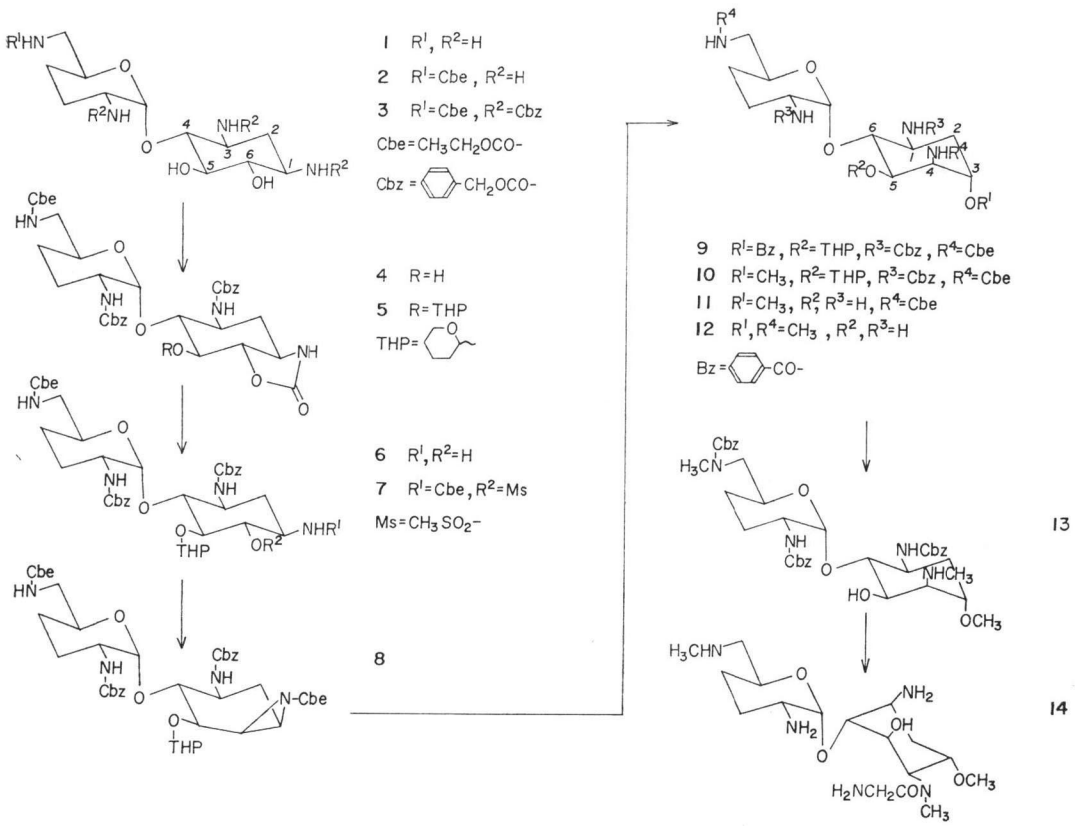
Sir:

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-ethoxycarbonyl-3′,4′-dideoxyneamine (**2**, 21% yield), $[\alpha]_D^{22}+73°$ (*c* 0.67, H_2O). The free amino groups of **2** were protected with benzyloxycarbonyl group by reaction with benzyl S-4,6-dimethylpyrimid-2-ylthiocarbonate in 80% aqueous methanol overnight at room temperature to yield 1,3,2″-tri-N-benzyloxycarbonyl-6′-N-ethoxycarbonyl-3′,4′-dideoxyneamine monohydrate (**3**, 89% yield), $[\alpha]_D^{23}+35°$ (*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-2*H*-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%

Scheme 1. Synthesis of istamycin A

In this paper, the numberings of the 1,3-diaminocyclitol and 1,4-diaminocyclitol are based upon those of streptamine and fortamine,[5] respectively.



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, $[\alpha]_D^{25}+60°$ (*c* 0.4, $CHCl_3$).

Removal of the O-benzoyl 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, $[\alpha]_D^{26}+31.5°$ (*c* 1, $CHCl_3$), PMR ($CDCl_3$), δ 3.35 (OCH_3). Successive removals of O-tetrahydropyranyl group in **10** by treatment with a mixture of acetic acid, methanol and water (7: 5: 3) at 50°C overnight and of N-benzyloxycarbonyl groups by catalytic hydrogenation with 5% palladium on carbon under atmospheric pressure for 2.5 hours gave the di-N-ethoxycarbonyl derivative (**11**). Compound **11** was reduced by diborane 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 (NH_4^+) resin using 0.4 N ammonia and found to be identical with deglycylistamycin A (named istamycin A_0) 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-hydroxysuccinimide 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 (NH_4^+) 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 fermentation[1] in all respects including antimicrobial activity.

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References

1) OKAMI, Y.; K. HOTTA, M. YOSHIDA, D. IKEDA, S. KONDO & H. UMEZAWA: New aminoglycoside antibiotics, istamycins A and B. J. Antibiotics 32: 964～966, 1979
2) IKEDA, D.: Synthetic studies on ribostamycin derivatives. p. 32, Ph. D. dissertation (Keio University), 1974
3) UMEZAWA, S.; T. TSUCHIYA, T. JIKIHARA & H. UMEZAWA: Synthesis of 3′,4′-dideoxyneamine active against kanamycin-resistant *E. coli* and *P. aeruginosa*. J. Antibiotics 24: 711～712, 1971
4) JIKIHARA, T.; T. TSUCHIYA, S. UMEZAWA & H. UMEZAWA: Studies on aminosugars. XXXV. Syntheses of 3′,4′-dideoxyneamine and 3′- and 4′-O-methylneamines. Bull. Chem. Soc. Jap. 46: 3507～3510, 1973
5) EGAN, R. S.; R. S. STANASZEK, M. CIROVIC, S. L. MUELLER, J. TADANIER, J. R. MARTIN, P. COLLUM, A. W. GOLDSTEIN, R. L. DEVAULT, A. C. SINCLAIR, E. E. FAGAR & L. A. MITSCHER: Fortimicins A and B, new aminoglycoside antibiotics. III. Structural identification. J. Antibiotics 30: 552～563, 1977