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TOTAL SYNTHESIS OF L-CAPREOMYCIDINE[1)]

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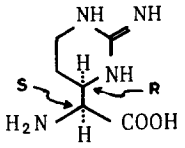
Capreomycidine (1) is a unique cyclic guanidino amino acid which was first isolated from the hydrolyzate of antibiotic capreomycin by Herr in 1962.[2)] In our studies on similar antibiotics, tuberactinomycins, the same amino acid was also found as one of the constituent amino acids of tuberactinomycin N and O.[3)]



(1)

Although, the chemical structure of capreomycidine was assigned by Herr[2)] and its stereochemistry was assumed by Bycroft *et al.*,[4)] the absolute configuration was first established by X-ray analysis of tuberactinomycin O.[3)]

DL-Capreomycidine had been already synthesized by Bycroft *et al.*,[5)] starting from 2-amino-4-methoxycarbonylmethyl-6-hydroxypyrimidine. According to this synthetic method, preparation of the natural form of capreomycidine could be practically difficult though not impossible in principle. In the present investigation, we attempted to synthesize an optically active L-capreomycidine through entirely different process. As a key intermediate for our synthesis, we chose β-hydroxy-L-ornithine derivative (7) obtained by enzymatic resolution of the synthetic racemate (5), and completed the synthesis by guanidination of β-amino-L-ornithine (12) derived from 5.

The synthetic route of β-hydroxy-L-ornithine derivative (7) was shown in Fig. 1. Thus, starting from diethyl acetal of β-aminopropionaldehyde (2), β-(benzyloxycarbonylimino)propionaldehyde (4) was condensed with N-pyruvylideneglycinatoaquocopper(II) according to the method of Ishido *et al.*,[6)]

to obtain 5 as a mixture of *threo* (5a) and *erythro* (5b)[7] in the ratio of 8 : 1, being estimated by amino acid analysis (55cm column, pH 5.28, 0.35 M sodium citrate buffer) of the hydrolyzate of the crude product. The *threo* isomer separated by fractional crystallization was then chloroacetylated followed by resolution by means of acylase.[8]

A synthetic process from δ-benzyloxycarbonyl-β-hydroxy-L-ornithine (7) thus obtained as far as L-capreomycidine, is outlined in Fig. 2. Conversion of hydroxyl group of 7 to amino group was carried out through an aziridine derivative (11). Thus, a N-tosyl derivative (8) was converted to an amide (9) in order to minimize β-elimination reaction during the following reaction.[9] The hydroxy group of 9 was mesylated to give 10 which was then treated with diethylamine to obtain the aziridine derivative (11).[10] After the aziridine ring of 11 had been opened by ammonolysis, benzyloxycarbonyl group was removed by hydrogenolysis to afford 12. Guanidination between two free amino groups in 12 was performed by use of cyanogen bromide. Finally, the product was hydrolyzed with hydrobromic acid to give 1. NMR spectrum of 1 was superimposable on that of the natural one, and diflavianate of 1 [Found: C, 37.87; H, 3.10; N, 13.70; S, 7.92%, Calcd. for $C_6H_{12}N_4O_2 \cdot 2C_{10}H_6N_2O_8S \cdot H_2O$: C, 38.15; H, 3.20; N, 13.69; S, 7.83%] was identical with the natural specimen in all respects as shown in Table 1.

Table 1. Comparisons of Synthetic and Natulal L-Capreomycidine Diflavianate

			Synthetic	Natural
mp (decomp.)			215-225°C	218-230°C
$[\alpha]_D^{50}$ (c 1, H_2O)			+5.1°	+5.4°
Rf	TLC	a)	0.13	0.13
		b)	0.50	0.50
	PC	c)	0.34	0.34
		d)	0.16	0.16
A.A.A.			58 min.	58 min.

Developing solvent: a) butanol-acetic acid-water(4:1:2:), b)phenol-water-28% ammonia(30:10:1), c) *t*-butanol-acetic acid-water(2:1:1), d) butanol-ethyl methyl ketone-28% ammonia-water(5:3:3:1). A.A.A.: amino acid analysis(7 cm column, pH 5.28, 0.35 M sodium citrate buffer).

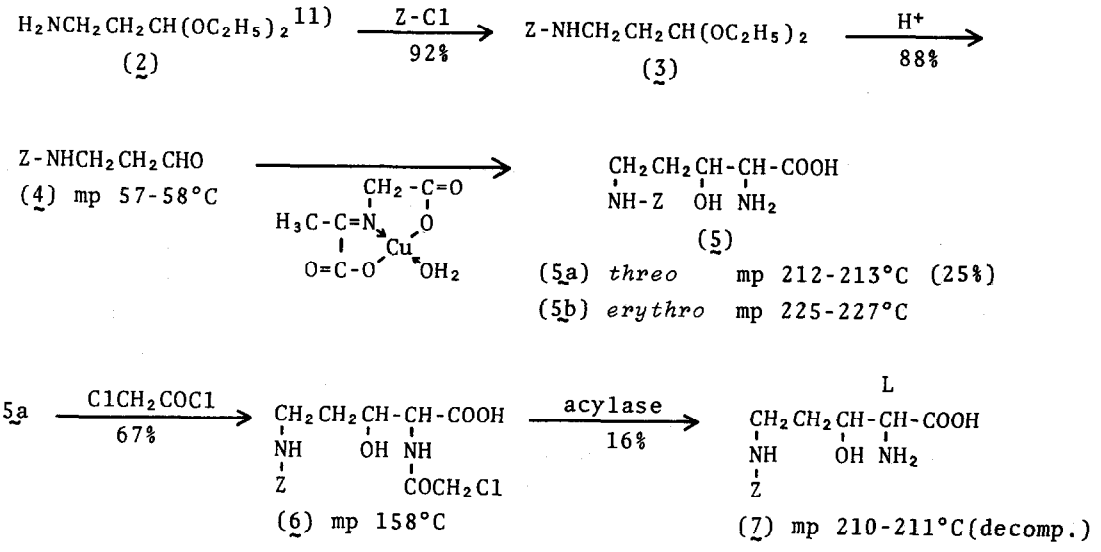


Fig. 1

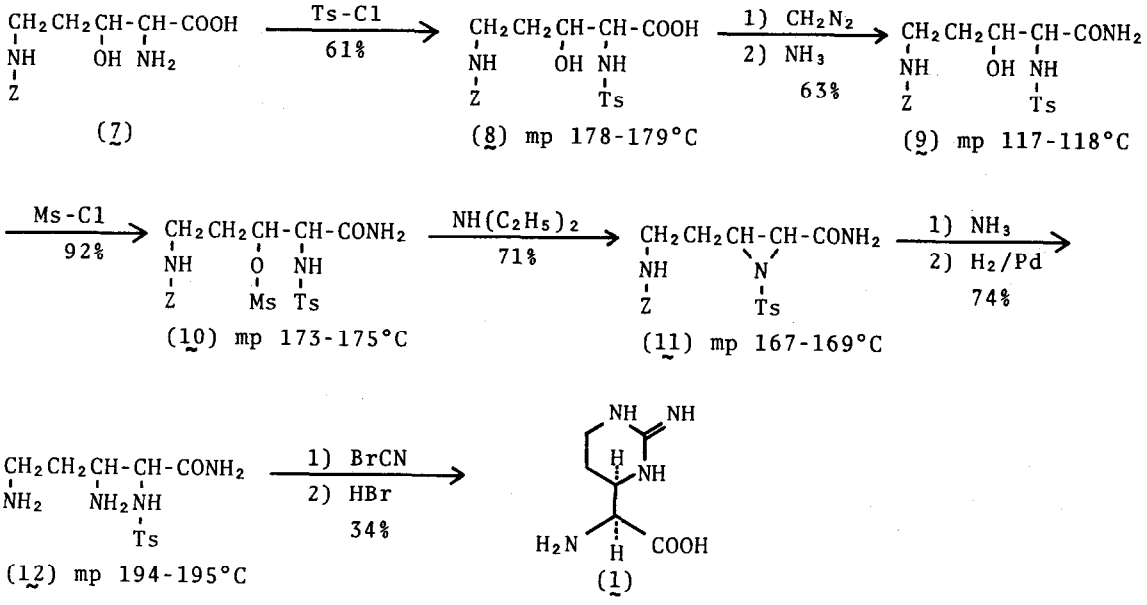


Fig. 2

Abbreviations; Z: benzyloxycarbonyl, Ts: *p*-toluenesulfonyl, Ms: methanesulfonyl.

REFERENCES AND FOOTNOTES

* To whom correspondence should be addressed.

1) Total synthesis of DL-capreomycidine as preliminary approach to that of L-isomer in the same synthetic principle was presented at the 34th Annual Meeting of the Chemical Society of Japan, Kanagawa, April, 1976, p 698.

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5) B. W. Bycroft, D. Cameron, and A. W. Johnson, *J. Chem. Soc. (C)*, 1971, 3040.

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7) Each authentic sample had been already obtained in our previous studies. a) S. Futagawa, T. Inui, and T. Shiba, *Bull. Chem. Soc. Jpn.*, 46, 3308 (1973). b) T. Wakamiya, T. Teshima, I. Kubota, T. Shiba, and T. Kaneko *ibid.*, 47, 2292 (1974).

8) A mixture of chloroacetyl derivative (6) and acylase in water (pH 7.2) was incubated at 37°C for 70h in the presence of Co^{++} as a catalyst. In the cases of N^{α}, N^{δ}-bis(chloroacetyl)-, N^{α},N^{δ}-diacetyl- and N^{α}-chloroacetyl-N^{δ}-phthalyl-β-hydroxyornithine, enzymatic resolution did not proceed smoothly.

9) Y. Nakagawa, T. Tsuno, K. Nakajima, M. Iwai, H. Kawai, and K. Okawa, *Bull. Chem. Soc. Jpn.*, 45, 1162 (1972).

10) Mesylation gave more desirable result than tosylation in view of the yield of 11.

11) Badische Anilin- & Soda-Fabrik (I. G. Farbenindustrie Akt. Ges. "In Auflösung") (Friedrich Becke, inventor). Ger. 845, 348, July 31, 1952 (Cl. 12q. 32_{01}).