

CHEMICAL STUDIES ON TUBERACTINOMYCIN. XVIII.¹
 SYNTHESSES OF DL-DIHYDROVIOMYCIDINE AND DL-VIOMYCIDINE.²

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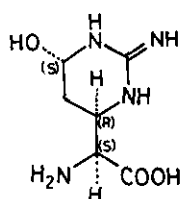
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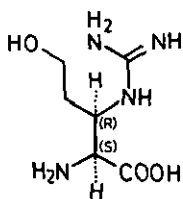
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Dihydroviomycinidine(2) and viomycinidine(3) were guanidino amino acids derived artificially from tuberactidine(1) in peptide antibiotics tuberactinomycin A and B(viomycin). The amino acids 2 and 3 of DL-forms were synthesized from common precursor, *threo*-2-amino-3,5-dihydroxypentanoic acid derivative. Guanidination of 3-hydroxyl group gave 2, while further oxidation of 5-hydroxyl group afforded 3. Both diflavianates of synthetic DL-2 and DL-3 were completely identical with those of the corresponding natural L-compounds in respect of tlc, pc, hplc, amino acid analysis, and nmr.

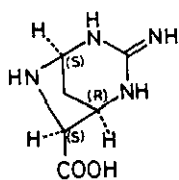
The presence of a cyclic guanidino amino acid tuberactidine(1) as one of the components in viomycin(tuberactinomycin B) which was a peptide antibiotic effective against tubercular bacilli had been presumed since 1968.³ Despite of many efforts to isolate this assumed amino acid, only the isolated was viomycinidine(3)⁴ which was later considered to be an artifact produced from tuberactidine in acid hydrolysis of the original antibiotic. Meanwhile, the absolute structure of viomycinidine was established by X-ray analysis.^{4f} On the other hand, when tuberactinomycin A



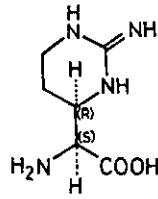
tuberactidine
1



dihydroviomycinidine
2



viomycinidine
3



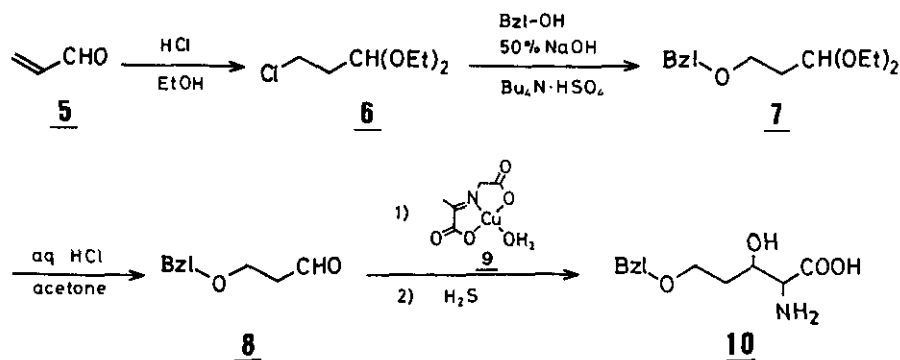
capreomycinidine
4

or viomycin was reduced with NaBH_4 and then immediately hydrolyzed, a second artifact, dihydroviomycinidine(2), was isolated.^{3b,5} These facts strongly suggested the assumption that an intact form of the guanidino amino acid in the original antibiotics should be tuberactidine from which viomycinidine could be formed

In 1970, we succeeded to isolate tuberactidine itself, for the first time, from tuberactinomycin A.⁵ The chemical and steric structures were then determined by nmr spectroscopy and ord measurement.⁵ Furthermore, recent X-ray analyses of viomycin⁶ and *o*-methyltuberactinomycin A⁷ ensured the absolute configuration of tuberactidine, supporting our previous results.

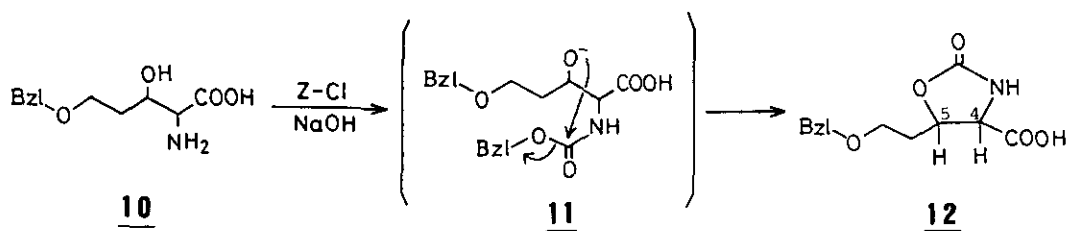
Syntheses of viomycinidine and dihydroviomycinidine seemed to be important not only to confirm the structures themselves but also to survey the possible way to synthesize tuberactidine. Synthesis of a similar cyclic guanidino amino acid capreomycinidine(4) was achieved in our previous studies on capreomycin or tuberactinomycin N and O.⁸ According to this strategy, first, we planned the synthetic routes for both viomycinidine and dihydroviomycinidine *via* β -hydroxyornithine and then 2-amino-3,5-dihydroxypentanoic acid. However, since we soon realized the difficulty of conversion of δ -amino group of β -hydroxyornithine into hydroxyl group, direct synthesis of 2-amino-3,5-dihydroxypentanoic acid derivative by coupling of 3-hydroxypropanal derivative with a glycine copper complex was newly exploited as shown in Scheme 1.

Acrolein(5) was converted into 3-chloropropanal diethyl acetal(6) by treatment with hydrogen chloride in ethanol.⁹ Modified Williamson ether synthesis using phase transfer catalyst¹⁰ was successfully applied to the preparation of 3-benzyl-oxypropanal diethyl acetal(7) from 6. The desired amino acid 10 was then prepared by aldol condensation of 3-benzyl-oxypropanal(8) derived from 7 with aqua[N-(1-



Scheme 1

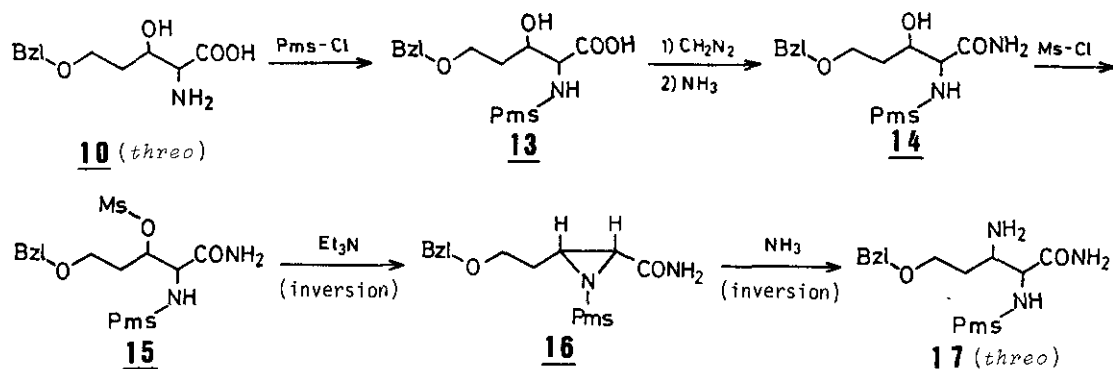
carboxylatoethylidene)glycinato]copper(II)(9).¹¹ In this reaction, the selective formation of a single diastereoisomer was confirmed by amino acid analysis, thin-layer chromatography(tlc), paper chromatography(pc), and high performance liquid chromatography(hplc). The stereochemistry of the product was determined by nmr study on its oxazolidone derivative by application of the confirmative method of configuration of vicinal amino alcohol developed in our laboratory.¹² Thus, the *trans* form derived from *threo* amino alcohol gives the coupling constant of about 5 Hz for C-4 and C-5 protons of oxazolidone ring while *cis* form from *erythro* amino alcohol shows around 10 Hz. Actually, the coupling constant of 5.8 Hz was observed on the oxazolidone derivative 12 prepared from 10 (Scheme 2). This clearly indicated that the compound 12 should be *trans* form. Therefore, the configuration of the hydroxy amino acid 10 was assigned to be *threo* form which was desirable for our purpose of preparations of viomycin and dihydroviomycin possessing the same stereochemistry.



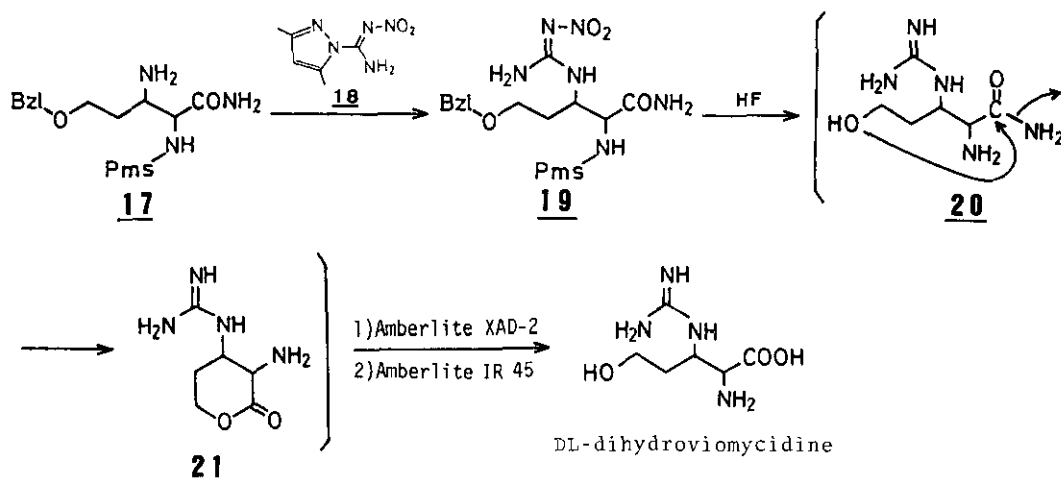
Scheme 2

3-Hydroxyl group was then converted into amino group with retention of the configuration by ammonolysis *via* aziridine as shown in Scheme 3. Thus, 2-amino group was first protected with *p*-tolylmethylsulfonyl(Pms)¹³ group. This protecting group is removable with anhydrous hydrogen fluoride without decomposition of the final product, dihydroviomycin, which was very sensitive to 47% hydrobromic acid used conventionally upon deprotection of *p*-toluenesulfonyl group. The carboxyl group of *p*-tolylmethylsulfonyl derivative 13 was then changed into the acid amide. Otherwise β -elimination reaction occurred readily by treatment of *O*-mesylate of β -hydroxy amino acid with base when the carboxyl group was free or esterified.¹⁴ For the *N*-protected acid amide 14, *O*-mesylation, aziridine formation, and ammonolysis were successively carried out to result in the production of 3-amino-5-benzyloxy-2-(*p*-tolylmethylsulfonylamino)pentanamide(17) in a satisfactory yield. Concerning the stereochemistry, it was established from

many elucidations^{8,14} that the configuration of α and β carbon atoms in such as compound 17 are certainly maintained as a result of double inversion throughout the course of reaction.

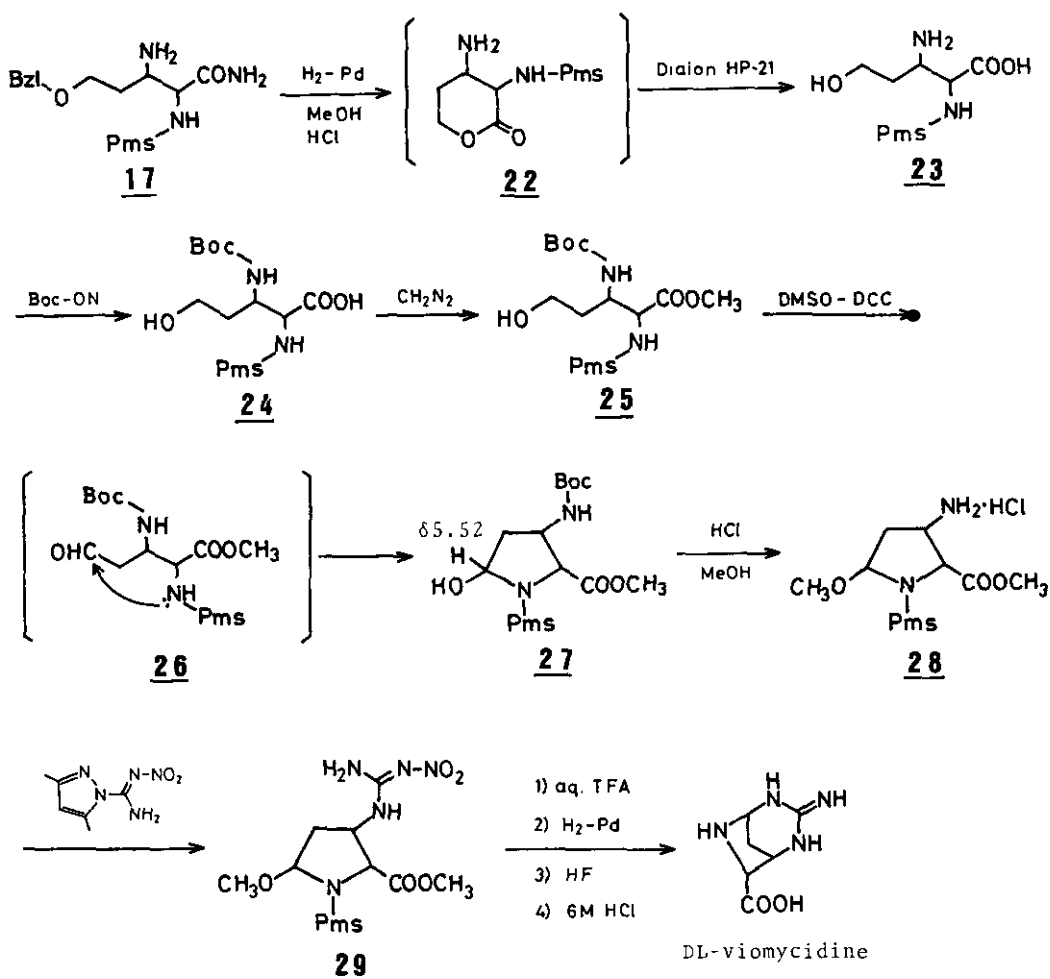


The diamino derivative 17 thus obtained was used to prepare dihydroviomycinide as mentioned in Scheme 4. Reaction of 17 with 3,5-dimethyl-1-nitroamidinopyrazole (18) to afford totally protected dihydroviomycinide(19). Subsequently, when the compound 19 was treated with anhydrous hydrogen fluoride, not only benzyl, nitro, and *p*-tolylmethylsulfonyl groups but also amide group were all removed at room temperature. The mechanism of the unexpected but desirable cleavage of the amide was satisfactorily explained by ready formation of δ -lactone under acidic condition *via* intramolecular *N,O*-acyl migration reaction as shown in parentheses of Scheme 4. The lactone was effectively hydrolyzed to give dihydroviomycinide of DL-form in the purification procedure on Amberlite XAD-2 and Amberlite IR-45 columns.



DL-Dihydroviomycin thus prepared was finally purified as crystalline diflavinate whose physicochemical properties were compared with those of natural L-dihydroviomycin. Although melting point of synthetic derivative differed from that of natural compound, tlc, pc, amino acid analysis, and proton nmr were completely identical with each other.

For the synthesis of viomycin, the compound 17 described above was also used as a key intermediate as outlined in Scheme 5. Reductive cleavage of benzyl in acidic medium was accompanied by elimination of the amide group like as in the synthesis of dihydroviomycin. Apparently, the intramolecular *N,O*-acyl migration reaction occurred under the acidic condition to give δ -lactone 22 showing the absorption at 1740cm^{-1} in ir spectrum. The lactone ring was easily opened by treat-



Scheme 5

ment on Diaion HP-21 column which was necessary to make free from NH_4Cl liberated as a result of deamidation. After the *t*-butoxycarbonylation of 3-amino group in the hydroxy amino acid 23 with 2-*t*-butoxycarbonyloxyimino-2-phenylacetonitrile (Boc-ON), carboxyl group of the compound 24 was immediately esterified with diazomethane to prevent relactonization. Oxidation of hydroxyl group in ester 25 successfully proceeded with dimethyl sulfoxide(DMSO) and dicyclohexylcarbodiimide(DCC)¹⁵ to produce 4-amino-2-hydroxy-5-methoxycarbonyl-1-(*p*-tolylmethysulfonyl)-pyrrolidine(27). The pyrrolidine ring in 27 corresponding to the five membered ring moiety in viomycin molecule is considered to be in equilibrium with aldehyde form 26 depending on the condition. However, the cyclic structure was substantiated in oily product 27 from nmr spectrum, in which methine proton on C-2 appeared at 5.52 ppm. Removal of *t*-butoxycarbonyl group and protection of carbinol group were carried out simultaneously with hydrogen chloride in methanol to give 4-amino-2-methoxy-5-methoxycarbonyl-1-(*p*-tolylmethysulfonyl)pyrrolidine(28). Nitro-guanidination of 4-amino group of 28 afforded the compound 29 whose protecting groups were successfully removed by treatment with aqueous TFA for *o*-methyl, hydrogenation for nitro, anhydrous hydrogen fluoride for *p*-tolylmethysulfonyl, and acid hydrolysis for methyl ester. Final acid treatment was also effective to form six membered ring in the molecule resulting in the production of viomycin, though yield was not satisfactorily good yet.

Synthetic DL-viomycin thus obtained was finally isolated and purified as crystalline diflavinate which was completely identical with natural L-viomycin diflavinate in respect of tlc, pc, amino acid analysis, and ^{13}C -nmr.

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