

TOTAL SYNTHESIS OF POLYOXIN J\*

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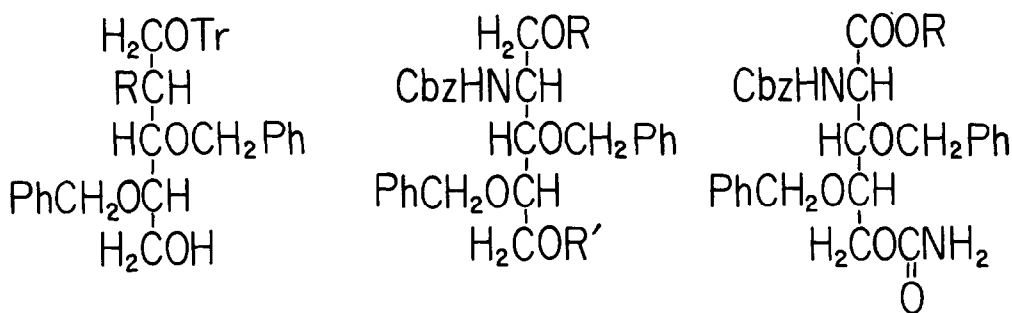
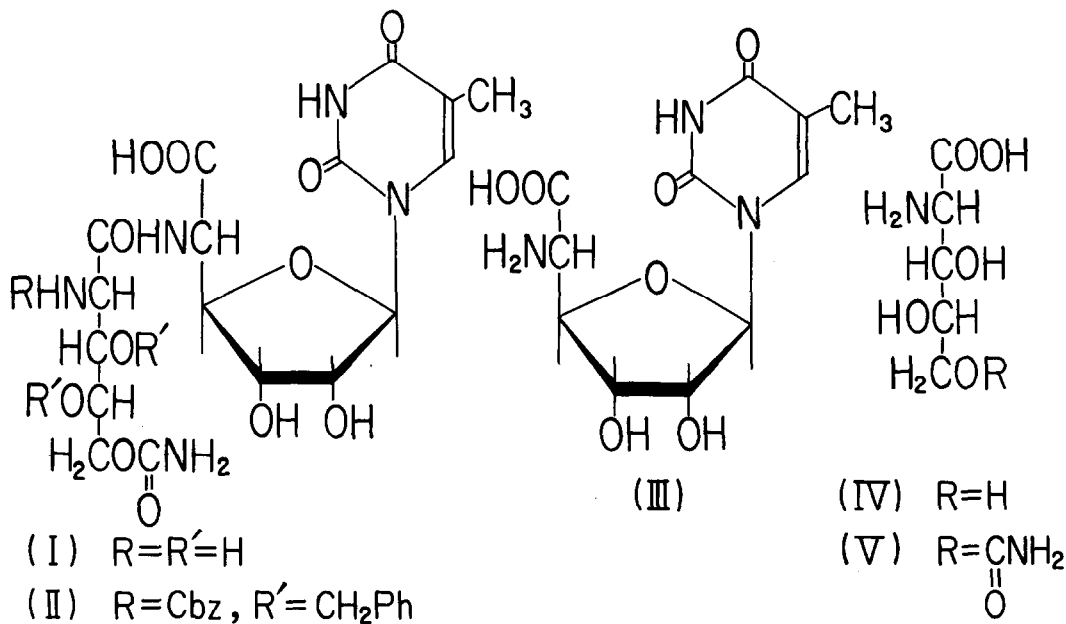
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The polyoxin complex is an excellent agricultural fungicide which was discovered in the culture broths of *streptomyces cacaoi var asoensis*.<sup>1)</sup> Several polyoxins which have the close structural relations to each other have been isolated from the complex and designated alphabetically.<sup>2)</sup>

In the previous papers of this series, we have reported the preparations of the constituent fragments of polyoxin J; namely the syntheses of 1-(5'-amino-5'-deoxy- $\beta$ -D-allofuranuronosyl)-thymine (Deoxy Polyoxin C, III),<sup>3)</sup> 2-amino-2-deoxy-L-xylonic acid (Polyoxamic Acid, IV)<sup>4)</sup> and 2-amino-5-O-carbamoyl-2-deoxy-L-xylonic acid (5-O-Carbamoyl-polyoxamic Acid, V).<sup>5)</sup> Now, we wish to describe the total synthesis of polyoxin J (I), which may help the syntheses of other polyoxins.

As reported in the preceding paper,<sup>5)</sup> 2-azido-3,4-di-O-benzyl-2-deoxy-1-O-trityl-L-xylitol (VI) was prepared from 1,2-O-isopropylidene- $\alpha$ -L-sorbopyranose *via* several steps of reactions. Treatment of VI with  $\text{LiAlH}_4$  in tetrahydrofuran led to reduction of the azido group, giving a syrupy amino compound VII. Without purification, VII was treated in aqueous methanol with benzyloxycarbonyl chloride (30% toluene solution) under the basic condition which was kept by dropwise addition of NaOH in aqueous methanol. The product was chromatographed on silica gel (benzene-ether) to give syrupy 3,4-di-O-benzyl-2-benzyloxycarbonylamino-2-deoxy-1-O-trityl-L-xylitol (VIII),  $[\alpha]_D^{22} -12^\circ$  ( $c$  0.84,  $\text{CHCl}_3$ );  $\nu_{\text{max}}^{\text{nujol}} \text{ cm}^{-1}$ :

\* Syntheses with Azido Sugars. Part IX



Tr=trityl, Ph=phenyl, Cbz=benzyloxycarbonyl

3450 (NH and OH), 1720 (C=O), in a yield of 71% on the basis of VI used. Compound VIII was treated in pyridine with *p*-nitrophenyl chloroformate to afford a syrupy 5-O-(*p*-nitrophenoxycarbonyl) derivative IX,  $[\alpha]_D^{22} -11^\circ$  ( $c$  1.69,  $\text{CHCl}_3$ );  $\nu_{\text{max}}^{\text{film}} \text{ cm}^{-1}$ : 3420, 3300 (NH), 1770 (C=O of the *p*-nitrophenoxycarbonyl group), 1720-1695 (C=O of the benzyloxycarbonyl group). Treatment of IX in dichloromethane with methanolic ammonia led to replacement of the *p*-nitrophenoxy group with an amino group, giving 5-O-carbamoyl derivative (X),  $[\alpha]_D^{22} +4^\circ$  ( $c$  1.49,  $\text{CHCl}_3$ );  $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$ : 3500, 3450, 3370 (NH and  $\text{NH}_2$ ), 1735-1700 (C=O), as a glass-like compound in a yield of 78% after chromatographic purification. The trityl group of X was removed by treatment with aqueous acetic acid (80%) at 80°C to give syrupy 3,4-di-O-benzyl-2-benzyloxycarbonylamino-5-O-carbamoyl-2-deoxy-L-xylitol (XI),  $[\alpha]_D^{25} +29^\circ$  ( $c$  0.88,  $\text{CHCl}_3$ );  $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$ : 3500-3350 (OH, NH, and  $\text{NH}_2$ ), 1735-1690 (both C=O).

A solution of XI in acetone was treated with  $\text{CrO}_3$  in aqueous sulfuric acid (7 N) at room temperature for 50 mins to afford 3,4-di-O-benzyl-2-benzyloxycarbonylamino-5-O-carbamoyl-2-deoxy-L-xylonic acid (XII),  $[\alpha]_D^{25} +32^\circ$  ( $c$  0.94,  $\text{CHCl}_3$ );  $\nu_{\text{max}}^{\text{film}} \text{ cm}^{-1}$ : 3500-3350 (NH and  $\text{NH}_2$ ), 2900-2500 (COOH), 1730-1695 (all C=O), in good yield. In the presence of dicyclohexylcarbodiimide, XII was esterified at 0°C in ethyl acetate with *N*-hydroxysuccinimide. The resulting *N*-hydroxysuccinimide ester (XIII) was immediately used for the next coupling reaction without purification.

Deoxy polyoxin C (III)<sup>3)</sup> was converted in water into triethylammonium salt by addition of stoichiometric amount of  $\text{Et}_3\text{N}$ . To this solution was added a solution of XIII in dimethyl formamide. After the mixture was kept at room temperature over a period of 20 hrs, it was treated with Dowex 50 ( $\text{H}^+$ ) and chromatographed on silica gel ( $\text{CHCl}_3\text{-CH}_3\text{OH-CH}_3\text{COOH}$ ) to give a mixture of the coupled product (II) and *N*-hydroxysuccinimide. The mixture was hydrogenated in aqueous methanol with Pd-C (10%) and chromatographed on Avicel (n-butanol-acetic acid-water) to afford Polyoxin J as a slightly colored powder. For further purification, this specimen was adsorbed on carbon. After the carbon was washed with a small amount of water, it was eluted with aqueous acetone (20%)

to afford pure I,  $[\alpha]_D^{23} +33^\circ$  ( $c$  0.75,  $H_2O$ ), in white amorphous form.<sup>6)</sup> This specimen gave satisfactory results of elemental analyses after drying *in vacuo* at 100°C for 4 hrs. Chromatographic behaviors of the prepared I on microcrystalline cellulose (three different kinds of solvent systems) were identical with those of authentic specimen. The prepared I also showed equivalent inhibitions to those of natural Polyoxin J against several species of phytopathogenic fungi in conventional agar dilution assay.

Overall yield was 28% on the basis of XII through the coupling reaction, removal of the protecting groups, and purification of the resulting I.

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#### REFERENCES AND FOOTNOTE

- 1) S. Suzuki, K. Isono, J. Nagatsu, T. Mizutani, K. Kawashima, and T. Mizuno, *J. Antibiot. (Tokyo)*, A18 131 (1965).
- 2) K. Isono, K. Asahi, and S. Suzuki, *J. Am. Chem. Soc.*, 91 7490 (1969).
- 3) H. Ohruai, H. Kuzuhara, and S. Emoto, *Tetrahedron Letters*, 1971 4267.
- 4) H. Kuzuhara, H. Ohruai, and S. Emoto, *Agr. Biol. Chem. (Tokyo)*, 37 949 (1973).
- 5) H. Kuzuhara and S. Emoto, *Tetrahedron Letters*, 1973, preceding paper.
- 6) Authentic I,  $[\alpha]_D^{23} +31^\circ$ , from natural source is also amorphous.