Synthesis in Nucleoside Antibiotics

Part VI. Synthesis of 4-Amino-4-deoxy- α -D-galacturonic Acid and 4-Amino-4-deoxy- α -D-glucuronic Acid Derivatives[†]

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Blastisidin S is an antibiotic first isolated by Yonehara and his associates¹⁾ from culture broths of *Streptomyces griseochromogenes*. It markedly inhibits the propagation of rice blast disease caused by *Piricularia oryzae*.²⁾ The structure was elucidated by Yonehara,³⁾ Ôtake *et al.*⁴⁾ and the absolute configuration was determined to be 1-(1'-cytosinyl)-4-[L-3'-amino-

5'-(1''-N-methylguanido)-valerylaminol]-1,2,3,4-tetra-deoxy- β -D-*erythro*-hex-2-ene uronic acid.⁵⁾ Controlled acid hydrolysis of this compound gave two components named blastidic acid (ϵ -N-methyl- β -arginine) and cytosinine respectively. The structure of cytosinine contains a 4-amino-4-deoxy-D-*erythro*-hex-2-ene uronic acid moiety. It has also been shown that

FIG. 1. The Synthetic Scheme of 4-Aminopyranuronate Derivatives.

[†] This work was presented in part at the Annual Meeting of the Agricultural Chemical Society of Japan, Fukuoka, April 1970 (see Abstr. Paper, p. 64).

1) S. Takeuchi, K. Hirayama, K. Ueda, H. Sakai and H. Yonehara, *J. Antibiot.*, **11A**, 1 (1958).

2) T. Misato, I. Ishii, M. Asakawa, Y. Okimoto and K. Fukunaga, *Ann. Phytopath. Soc.*, **24**, 302, 307 (1959).

3) H. Yonehara, S. Takeuchi, N. Ôtake, T. Endô, Y. Sakagami and Y. Sumiki, *J. Antibiot.*, **16A**, 195 (1963).

4) N. Ôtake, S. Takeuchi, T. Endô and H. Yonehara, *Tetrahedron Lett.*, **1965**, 1405, 1411; *Agr. Biol. Chem.*, **30**, 126, 132 (1966).

5) H. Yonehara, N. Ôtake, *Tetrahedron Lett.*, **1966**, 3785.

gougerotin contains a 4-amino-4-deoxy-D-glucopyranuronic acid moiety.⁶⁾

Recently, Fox and his coworkers reported the synthesis of methyl 4-amino-4-deoxy- α -D-glucopyranosiduronic acid⁷⁾ and its cytosine nucleoside.⁸⁾ In the course of the synthetic studies of antibiotics, we have also synthesized independently the *p*-toluenesulfonic acid salt of methyl (methyl 4-amino-2,3-di-O-benzoyl-4-deoxy- α -D-glucopyranosid) uronate and, in addition, the *p*-toluenesulfonic acid salt of methyl (methyl 4-amino-2,3-di-O-benzoyl-4-deoxy- α -D-galactopyranosid) uronate, starting from D-galactose and D-glucose, respectively. We now wish to describe briefly the synthesis. The synthetic scheme is shown in Fig. 1.

In the preparation of 4-amino-4-deoxy- α -D-

galacturonic acid derivatives, methyl 4,6-O-benzylidene- α -D-glucopyranoside prepared from D-glucose was first converted to the 2,3-di-O-acetate (I), 2,3-di-O-benzoate (II), and 2,3-di-O-benzyl ether (III). After the removal of the benzylidene group in boiling 80% aqueous acetic acid, each product was selectively tritylated to give 6-O-trityl ethers, respectively. Methanesulfonylation of each trityl ether yielded methyl 2,3-di-O-acetyl-4-O-mesyl-6-O-trityl- α -D-glucopyranoside (IV), mp 196~198°C, methyl 2,3-di-O-benzoyl-4-O-mesyl-6-O-trityl- α -D-glucopyranoside (V), mp 176~177°C, and methyl 2,3-di-O-benzyl-4-O-mesyl-6-O-trityl- α -D-glucopyranoside (VI),⁹⁾ mp 152~153°C, in an usual way. Treatment of the latter two 4-O-mesyl derivatives (V and VI) with sodium

FIG. 2. NMR Spectrum of 4-Azidoglucuronate Derivative (XIV) in CDCl_3 (60 MHz).

6) J. J. Fox, Y. Kuwada and K. A. Watanabe, *Tetrahedron Lett.*, **1968**, 6029.

7) M. P. Kotick, R. S. Klein, K. A. Watanabe and J. J. Fox, *Carbohydr. Res.*, **11**, 369 (1969).

8) K. A. Watanabe, M. P. Kotoick, and J. J. Fox, *J. Org. Chem.*, **35**, 231 (1970).

9) F.W. Lichtenthaler und P. Heidel, *Angew. Chem.*, **80**, 441 (1968).

azide in refluxing *N,N*-dimethylformamide for 6 hr caused almost quantitative liberation of the mesyl group, giving 4-azido compound (VII), mp 86~88°C, and VIII, mp 52~53°C, but the azidation of IV under the above conditions gave fairly low yield (yield, 70%, 90% and 40%, respectively).

After removal of the trityl group in boiling 50% acetic acid, the resulting methyl 4-azido-2,3-di-*O*-benzoyl-4-deoxy- α -D-galactopyranoside, $[\alpha]_D^{18} + 56^\circ$ ($c=1.10$ chloroform), was oxidized into methyl 4-azido-2,3-di-*O*-benzoyl-4-deoxy- α -D-galacturonic acid with potassium permanganate¹⁰⁾ in a solution of acetone-acetic acid-water (4:4:1 v/v) at room temperature for 3 days. Subsequent esterification of the powdery product in boiling methanol containing a catalytic amount of acetyl chloride af-

forded methyl (methyl 4-azido-2,3-di-*O*-benzoyl-4-deoxy- α -D-galactopyranosid) uronate (IX), $[\alpha]_D^{18} + 93^\circ$ ($c=1.16$ chloroform). The methyl uronate (IX) was treated with acetic anhydride containing 2% sulfuric acid to give methyl (1-*O*-acetyl-4-azido-2,3-di-*O*-benzoyl-4-deoxy- α -D-galactopyranosid) uronate (X), mp 166~168°C, $[\alpha]_D^{18} + 100^\circ$ ($c=0.77$ chloroform). Also catalytic hydrogenation of IX in the presence of 10% palladium on charcoal in methanol afforded the 4-amino uronate. Treatment of the 4-amino uronate with a solution of ether saturated with *p*-toluenesulfonic acid gave the *p*-toluenesulfonic acid salt of methyl (methyl-4-amino-2,3-di-*O*-benzoyl-4-deoxy- α -D-galactopyranosid) uronate (XI), mp 122~125°C, $[\alpha]_D^{18} + 136^\circ$ ($c=1.04$ methanol).

On the other hand, in the preparation of

FIG. 3. NMR Spectrum of 4-Azidogalacturonate Derivative (IX) in CDCl_3 (60 MHz).

10) M. Stacey and P.I. Wilson, *J. Chem. Soc.*, **1944**, 587.

methyl 4-amino-4-deoxy- α -D-glucuronic acid derivatives, methyl 2,3-di-O-benzoyl-6-O-trityl- α -D-galactopyranoside, mp 117~119°C, $[\alpha]_D^{18} + 166^\circ$ ($c=1.66$ chloroform), was converted to methyl 2,3-di-O-benzoyl-4-O-mesyl-6-O-trityl- α -D-galactopyranoside (XII), mp 108~109°C, $[\alpha]_D^{18} + 78^\circ$ ($c=1.25$ chloroform). Treatment of the compound XII with sodium azide in refluxing N,N-dimethylformamide for 6 hr gave methyl 4-azido-2,3-di-O-benzoyl-6-O-trityl-4-deoxy- α -D-glucopyranoside (XIII), 71 166~167°C, $[\alpha]_D^{18} + 115^\circ$ ($c=1.37$ chloroform), in a yield of 60%. Detritylation of XIII in 50% acetic acid afforded methyl 4-azido-2,3-di-O-benzoyl-4-deoxy- α -D-glucopyranoside, $[\alpha]_D^{18} + 189^\circ$ ($c=1.19$ chloroform). Oxidation of this compound with similar conditions described, followed by esterification, afforded methyl (methyl 4-azido-2,3-di-O-benzoyl-4-deoxy- α -D-glucopyranosid) uronate (XIV)⁷¹, $[\alpha]_D^{18} + 154^\circ$ ($c=1.30$ chloroform). Hydrogenation of XIV with 10% palladium on charcoal gave the 4-

amino derivative. Treatment of the 4-amino derivative with a solution of ether saturated with *p*-toluenesulfonic acid gave the *p*-toluenesulfonic acid salt of methyl (methyl-4-amino-2,3-di-O-benzoyl-4-deoxy- α -D-glucopyranosid) uronate (XV), mp 201~203°C, $[\alpha]_D^{18} + 114$ ($c=1.22$ methanol).

NMR spectral data (in CDCl₃) establish the *gluco*-configuration (see Fig. 2) for H-4 in the 4-azido derivative (XIV) derived from 4-mesyl galactoside (XII) and the *galacto*-configuration (see Fig. 3) for H-4 in the 4-azido derivative (IX) derived from 4-mesyl glucoside (V). Namely, the signal for H-3 in XIV appeared at δ 5.90 as a triplet ($J_{2,3} \approx J_{3,4} \approx 9.5$ Hz) and that for H-3 in IX appeared at δ 5.60 as a quartet ($J_{2,3} \approx 9.5$ Hz, $J_{3,4} \approx 3.5$ Hz).

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