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SYNTHESIS OF 5-O-CARBAMOYL-POLYOXAMIC ACID*

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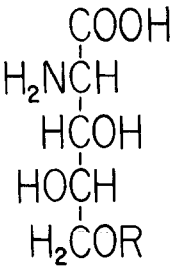
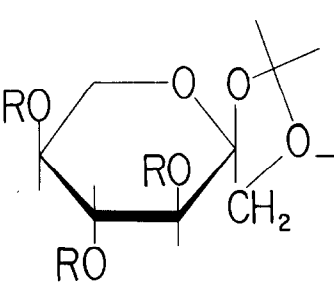
In the course of our study directed toward the total synthesis of Polyoxin J which is a member of the unique antibiotics, Polyoxin complex,[1] we have succeeded in syntheses of its constituent fragments; namely 1-(5'-amino-5'-deoxy-β-D-allofuranuronosyl)-thymine[2] and 2-amino-2-deoxy-L-xylonic acid (I)[3] which is designated as Polyoxamic acid.[1] Polyoxamic acid (I) also exists in Polyoxin A, B, D, F, H, and L and, in all polyoxins, 5-hydroxyl group of I is carbamoylated. Preparation of 5-O-carbamoyl-polyoxamic acid (II) from I is expected to encounter many difficulties because selective carbamoylation of such polyhydroxyl amino acid will require many steps of reactions, which may be accompanied with undesirable side reactions such as racemization, lactonization and elimination.

We wish to describe here synthesis of II in completely different way from our preparation of I.[3] The starting material, 1,2-O-isopropylidene-α-L-sorbopyranose[4] (III), was fully mesylated to afford crystalline trimesylate (IV), mp 125-7°C; $[\alpha]_D^{24}$ -41° (*c* 0.87, $CHCl_3$); δ ($CDCl_3$) ppm: 5.09 (H-4, $J_{3,4}=J_{4,5}=$ 9 Hz). Treatment of IV with an equivalent of NaN_3 in hexamethylphosphoric triamide gave a syrupy monoazido compound in 80% yield. On the basis of the analysis of its nmr spectrum, the compound was elucidated to be 5-azido-5-deoxy-1,2-O-isopropylidene-3,4-di-O-mesyl-D-fructopyranose (V),[5] $[\alpha]_D^{23}$ -107° (c 3.47, $CHCl_3$); ν_{max}^{film} cm^{-1}: 2100 (N_3); δ ($CDCl_3$) ppm: 5.16 (H-4, $J_{3,4}$=10 Hz, $J_{4,5}$=3.5 Hz). Compound V was heated under reflux in aqueous p-dioxane with KOH to give a

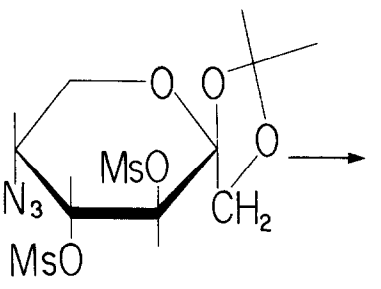
* Syntheses with Azido Sugars. Part VIII.



(Ⅰ) R=H
(Ⅱ) R=CNH_2 (O)



(Ⅲ) R=H
(Ⅳ) R=Ms



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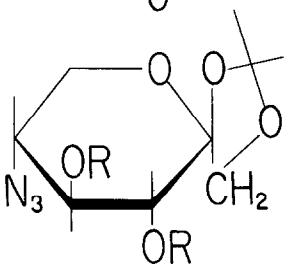
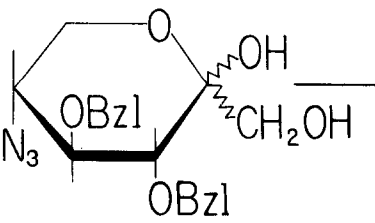


(Ⅵ) R=H
(Ⅶ) R=Ac
(Ⅷ) R=Bzl



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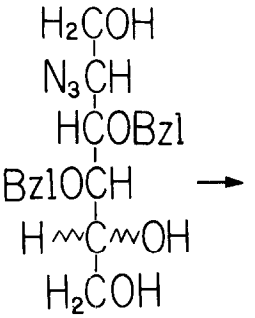

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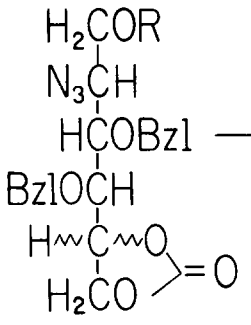
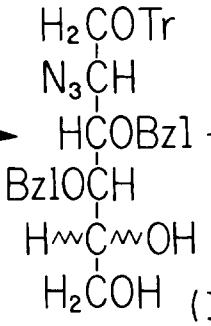


(Ⅺ) R=H
(Ⅻ) R=Tr



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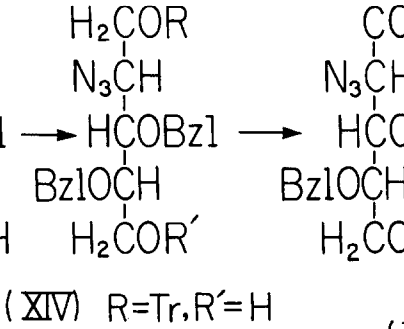
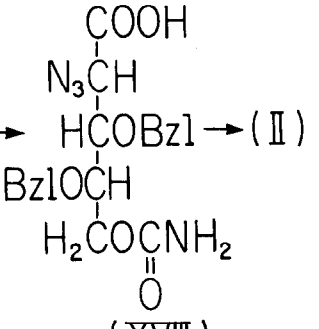


(ⅩⅣ) R=Tr, R′=H
(ⅩⅤ) R=Tr, R′=CO (O) $C_6H_4NO_2$
(ⅩⅥ) R=Tr, R′=CNH_2 (O)
(ⅩⅦ) R=H, R′=CNH_2 (O)



(ⅩⅧ)

(Ⅱ)

Ac=acetyl, Bzl=benzyl
Ms=methanesulfonyl, Tr=trityl

dihydroxy compound in 55% yield. In order to clarify its configuration, the dihydroxy compound was acetylated in the usual way to give a diacetate. Nmr spectrum of the diacetate revealed that it was 3,4-di-O-acetyl-5-azido-5-deoxy-1,2-O-isopropylidene-β-D-sorbopyranose (VII), mp 89-92°C; $[\alpha]_D^{25}$ -34° (*c* 0.61, $CHCl_3$); δ ($CDCl_3$) ppm: 4.93 (H-4, $J_{3,4}=J_{4,5}=7$ Hz). Therefore, the corresponding dihydroxy compound was identified with 5-azido-5-deoxy-1,2-O-isopropylidene-β-D-sorbopyranose (VI),[6] mp 100-102°C; $[\alpha]_D^{22}$ -72° (*c* 1.74, $CHCl_3$); ν_{max}^{KBr} cm^{-1}: 3580, 3400 (OH), 2100 (N_3). Compound VI was perbenzylated by the treatment with powdered KOH and benzyl chloride to afford a dibenzyl compound (VIII), mp 57-62° C; $[\alpha]_D^{19}$ +80° (*c* 1.85, $CHCl_3$); ν_{max}^{KBr} cm^{-1}: 2100 (N_3), 1500 (benzene). The isopropylidene group of VIII was hydrolyzed with sulfuric acid in aqueous isopropanol to give 5-azido-3,4-di-O-benzyl-5-deoxy-D-sorbopyranose (IX), $[\alpha]_D^{22}$ +46° (*c* 0.48, $CHCl_3$, no mutarotation); ν_{max}^{film} cm^{-1}: 3450 (OH), 2100 (N_3), 1500 (benzene).

As described in the previous paper of this series,[7] sodium borohydride can reduce in methanol selectively hemiacetals without affecting a co-existing azido group under the restricted condition. Although this selective reduction was applied to IX, it did not proceed smoothly but gave a lot of products. In diglime, however, sodium borohydride smoothly reduced at 0°C the hemiketal of IX to afford a couple of diastereomers of azido-polyols (X, mixture), ν_{max}^{film} cm^{-1}: 3400 (OH), 2100 (N_3). The next four steps of reactions were carried out with a mixture of two diastereomers. For protection of vicinal diols, X was treated in a mixture of chloroform and pyridine at -10°C with a large excess of carbonyl chloride and, after a while, the mixture was diluted with water. As only 1-O-chlorocarbonate formed was hydrolyzed with water, the product of the above reaction was 5,6-O-carbonate (XI, quantitative yield), ν_{max}^{film} cm^{-1}: 3500 (OH), 2100 (N_3), 1790 (C=O). Compound XI was tritylated to give 1-O-trityl derivative (XII), which was then treated with sodium methylate for hydrolysis of the carbonate to afford a diol (XIII), ν_{max}^{film} cm^{-1}: 3450 (OH). The vicinal diol of XIII was cleaved at 0°C with sodium periodate and the resulting aldehyde was immediately reduced in methanol at 0°C with sodium borohydride to give syrupy 2-azido-3,4-di-O-benzyl-2-deoxy-1-O-trityl-L-xylitol (XIV), $[\alpha]_D^{20}$ +15° (*c* 1.19, $CHCl_3$), ν_{max}^{film} cm^{-1}: 3470 (OH), 2100 (N_3). Compound XIV was treated in pyridine with

excess of *p*-nitrophenyl chloroformate and then chromatographed on silica gel (benzene) to give 5-O-*p*-nitrophenoxycarbonate (XV), mp 106-108°C; $[\alpha]_D^{23}$ +8° (*c* 1.83, $CHCl_3$); ν_{max}^{film} cm^{-1}: 1770 (C=O), 1525, 1350 (NO_2). *p*-Nitrophenoxy group of XV was replaced with amine by treatment of XV in dichloromethane with methanolic ammonia to give 5-O-carbamate (XVI), mp 45-50°C; $[\alpha]_D^{26}$ +17° (*c* 0.86, $CHCl_3$); ν_{max}^{film} cm^{-1}: 3510, 3380 (NH_2), 1730 (C=O), 1600 (NH_2, benzene). Compound XVI was treated with aqueous CF_3COOH (90% v/v) for 5 mins to give a detritylated compound (XVII), $[\alpha]_D^{25}$ +12° (*c* 0.92, $CHCl_3$); ν_{max}^{film} cm^{-1}: 3500-3350 (OH, NH), 2100 (N_3), 1715 (C=O), 1600 (NH_2, benzene), which was oxidized in acetone with CrO_3 in dilute sulfuric acid (7 N) at room temperature for 50 mins. The oxidization product was chromatographed on silica gel (benzene-acetone-acetic acid) to afford syrupy 2-azido-3,4-di-O-benzyl-5-O-carbamoyl-2-deoxy-L-xylonic acid (XVIII), $[\alpha]_D^{25}$ +15° (*c* 1.04, $CHCl_3$); ν_{max}^{film} cm^{-1}: 3500, 3370, 3200 (NH_2), 2880-2550 (COOH), 2100 (N_3), 1730-1690 (both C=O), 1590 (NH_2, benzene), in 63% yield. Compound XVIII was catalitically reduced with Pd-C (10%) in two steps; firstly in aqueous acetic acid and secondly in water to give crystalline 5-O-carbamoyl-polyoxamic acid (II), mp 210°C (Dec.); $[\alpha]_{365}^{22}$ +23° (*c* 1.1, H_2O). {authentic specimen,[8] mp 214-215°C (Dec.), $[\alpha]_{365}^{22}$ +22°}. Chromatographic behaviors and ir spectrum of II were completely identical with those of the authentic specimen derived from natural polyoxins.

REFERENCES AND FOOTNOTES

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2) H. Ohrui, H. Kuzuhara, and S. Emoto, Tetrahedron Letters, 1971 4267.
3) H. Kuzuhara, H. Ohrui, and S. Emoto, Agr. Biol. Chem. (Tokyo), 37 949 (1973).
4) J. R. Patil and J. L. Bose, J. Ind. Chem. Soc., 43 161 (1966).
5) Replacements at a similar position of pentopyranosides were reported. See J. K. N. Jones et al., Canadian J. Chem., 44 79 (1966).
6) On the basis of the other experiments, it was confirmed that the conversion of V into VI proceeded *via* 3,4-anhydro-5-azido-5-deoxy-1,2-O-isopropylidene-β-D-psicopyranose. For similar example, see the reference cited in 5).
7) H. Kuzuhara, H. Ohrui, and S. Emoto, Agr. Biol. Chem. (Tokyo), 35 8 (1971).
8) offered by Dr. M. Uramoto, to whome thanks were due.