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NUCLEOSIDES LXVI. SYNTHETIC STUDIES ON NUCLEOSIDE ANTIBIOTICS. 4. SYNTHESIS OF METHYL 4-AMINO-2,3,4-TRIDEOXY-α-D-ERYTHRO-HEX-2-ENOPYRANOSIDURONIC ACID, THE CARBOHYDRATE MOIETY OF BLASTICIDIN S [1]

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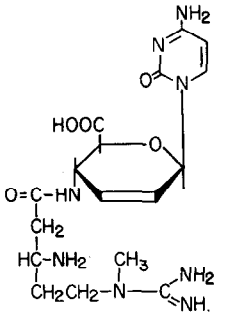
The chemistry and biochemistry of nucleoside antibiotics have recently received considerable attention [2]. Reports from our laboratory have described the syntheses of methyl 4-amino-4-deoxy-α-D-glucopyranosiduronic acid [3] and 1-(4-amino-4-deoxy-β-D-glucopyranosyluronic acid)cytosine [4] (C-substance), which are the carbohydrate and the nucleoside moieties of Gougerotin [5].

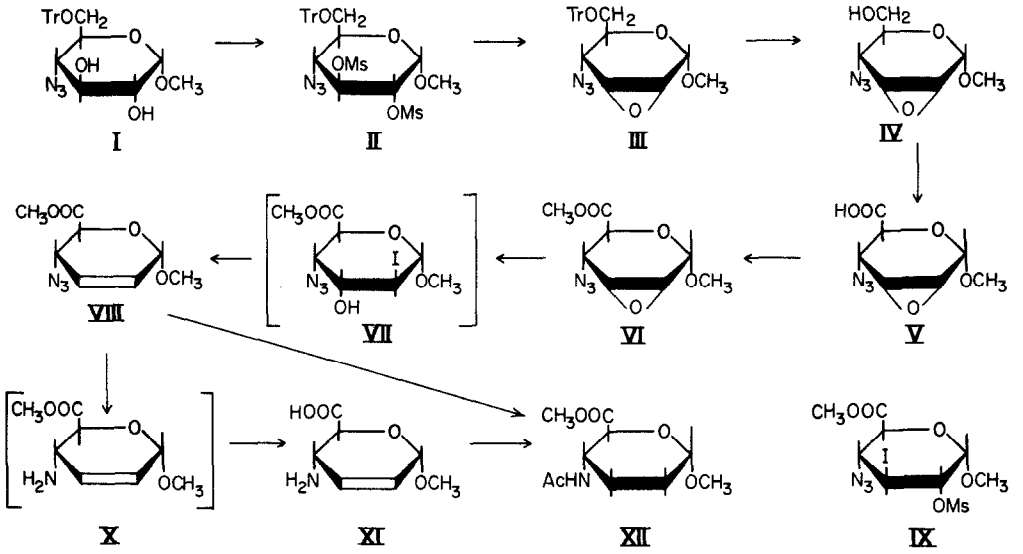


BLASTICIDIN S

Blasticidin S, a structurally-related antibiotic which is highly effective against rice blast disease, contains the nucleoside moiety, 1-(4-amino-2,3,4-trideoxy-β-D-erythro-hex-2-enopyranosyluronic acid)-cytosine [6]. In this report we deal with the synthesis of methyl 4-amino-2,3,4-trideoxy-α-D-erythro-hex-2-enopyranosiduronic acid (XI), the carbohydrate fragment of Blasticidin S. This constitutes the first synthesis in this new class of carbohydrates, the unsaturated amino sugars (see Flow Chart).

The 6-O-trityl-4-azido-α-D-glucoside (I) [3] was mesylated to II and converted into epoxide (III) with sodium methoxide in methanol. After de-tritylation of III in 80% HOAc, the product (IV) was oxidized with $KMnO_4$ [3] to the allouronic acid epoxide (V). Esterification of V with diazomethane afforded the ester (VI) which, after treatment with NaI in a mixture of HOAc and acetone containing a small amount of NaOAc [7], yielded a mixture of iodohydrins of the gluco and altro (VII) configuration in a ratio of ~ 1:2. Treatment of this mixture with mesyl chloride in pyridine [7] gave the olefin (VIII) as the major product along with the 2-O-mesyl-glúco iodohydrin IX. Separation of this mixture on a Silica Gel G column gave the olefin (VIII) as a mobile liquid and the iodo-

mesylate (IX) in crystalline form. The nmr spectrum of IX showed an anomeric doublet at δ = 4.94 and a quartet at δ = 4.72 ($J_{1,2}$ = 3.2, $J_{2,3}$ = 9.5 Hz), which established the gluco



FLOW CHART

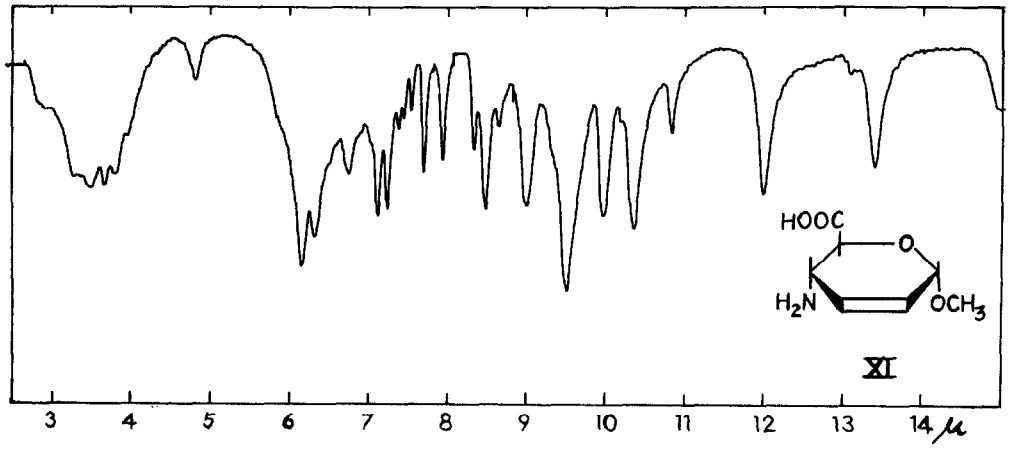


Fig. I

configuration for (IX) and, thereby, the allo configuration for epoxides III → VI. Additional evidence for the allo configuration of the epoxides is given in Table I [9,10].

Compound VIII, after reduction with sodium dithionite [11] followed by saponification, was converted to crystalline methyl 4-amino-2,3,4-trideoxy-α-D-erythro-hex-2-enopyranosiduronic acid (XI). The structure and configuration of olefins VIII and XI were established by nmr studies (see Table I). The low field signal integrated for two protons, confirming the presence of the 2,3-unsaturated structure and the large coupling exhibited by H4 and H5 ($J_{4,5}$ = 9.5 Hz) established the erythro (trans) configuration. The i.r. spectrum of VIII (λ_{max}^{KBr} 3.26-3.95, 4.78 and 6.13 μ, NH_3^+; 6.29 and 13.38 μ, COO^-) is typical of a free amino acid (Fig. I) [12]. Reduction of XI over platinum followed by acetylation with acetic anhydride in methanol and then esterification with diazomethane afforded XII in good yield.

To confirm that configurational change at C-4 or C-5, or both, had not occurred during the conversion of VIII → XI (particularly during the alkaline treatment of X) compound XII was also prepared in high yield directly by reduction of VIII over platinum followed by acetylation, using conditions under which isomerization would not occur.

TABLE I. PHYSICAL CONSTANTS AND NMR PARAMETERS * OF NEW COMPOUNDS

			Chemical Shifts(δ)						Approx. J value (Hz)			
Compound	mp	$[\alpha]_D^{23^o}$	H1	H2	H3	H4	H5	OCH_3	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
II	166-167	+105	5.15	5.07	4.70	4.17			3.0	9.0	9.0	9.0
III	102-103	+122	4.97	3.43	3.78	3.18	3.93	3.49	2.3	4.0	4.0	10.0
IV	67-68	+236	4.93					3.32	2.8			
V	136-138	+230	5.03			3.78	4.37	3.51	2.5			9.5
VI	66-67	+232	5.00			3.85	4.30	3.49	2.5			9.5
VIII		+201	4.99	5.90	6.01	4.32	4.18	3.37	1.2	10.0	1.0	9.2
IX	95-97	+ 89	4.94	4.71				3.51	3.5	10.0		
XI	>270(d.)	+30.5	5.12	6.04	6.04	3.97	4.20	3.48				10.5
XII	145-146	+ 87	4.81	1.7-2.0		4.0-4.3		3.38				

* All compounds listed herein gave satisfactory elemental analyses. Optical rotations were run at ~ 23° in $CHCl_3$ except compound XI which was run in water and compound VIII in methanol. Nmr solvents: compounds II and IV were run in DMSO-d_6; compound VIII in acetone-d_6; compound XI in D_2O; all others in $CDCl_3$.

Further studies on this class of carbohydrates, including the synthesis of nucleosides thereof, are underway in our laboratory.

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