STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESES OF THE NUCLEOSIDE ANTIBIOTICS, GOUGEROTIN AND BLASTICIDIN S†

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ABSTRACT

The structurally related cytosine nucleoside antibiotics, Gougerotin and Blasticidin S, discovered in Japan, have been the subject of intensive biochemical investigation. Both antibiotics inhibit protein synthesis on the aminoacyl-tRNA-ribosomal level and both inhibit the growth of certain viruses. Blasticidin S is a powerful agent against rice blast disease. For these and other considerations we embarked upon a programme directed toward the total synthesis and biological evaluation of pyrimidine nucleoside antibiotics related in structure to these antibiotics.

Hydrolysis of Gougerotin and Blasticidin S removes the dipeptidyl or aminoacyl moieties and affords the nucleoside components, C-substance and cytosinine, respectively. Studies resulting in the total synthesis of C-substance from D-galactose will be described involving the synthesis of 4-aminoglucosyluronic acids (a new class of carbohydrates) and nucleosides thereof. The synthesis of 2,3-unsaturated-4-amino sugars and their corresponding uronates will be given as well as progress achieved towards the synthesis of cytosinine which contains this unsaturated sugar moiety.

Studies in progress dealing with the linkage of amino acids to 4-amino sugar nucleosides will be discussed.

The structurally-related cytosine nucleoside antibiotics, Gougerotin[1] and Blasticidin S[2] (*Figure 1*), have been the subject of intensive investigation[3]. Both antibiotics inhibit protein synthesis on the aminoacyl-tRNA-ribosomal level[3]. Both antibiotics inhibit the growth of certain viruses[4]. Blasticidin S is a powerful agent against rice blast disease in Japan[5]. For these and other considerations we embarked upon a programme directed toward the total synthesis and biological evaluation of pyrimidine nucleoside antibiotics related in structure to Gougerotin and Blasticidin S. This lecture deals with progress achieved towards these goals.

Acid hydrolysis of Gougerotin removes the dipeptide, sarcosyl-D-serine, and affords the 4′-aminoglycosyluronic acid nucleoside, C-substance (*Figure 1*). Similarly, removal of the ε-*N*-methyl-β-arginine grouping by alkaline

† The authors dedicate this treatise to the memory of the late Frank L. Horsfall, Jr., M.D., in appreciation of his encouragement and support in this field of endeavour.

hydrolysis of Blasticidin S affords cytosinine. Both of these nucleoside hydrolysis products contain the hitherto unknown 4-amino-4-deoxy-glycosyluronic acid moieties. We undertook the synthesis of C-substance

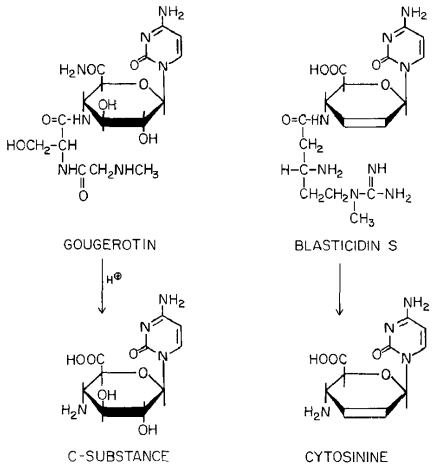

Figure 1

as our first objective with the hope that such studies would lead eventually to a total synthesis of Gougerotin, and analogues thereof, and would serve as a foundation for the more difficult task, namely, the synthesis of the 2,3-unsaturated amino sugar (a new class of carbohydrates) nucleosides (viz. cytosinine).

The first synthesis[6] of a 4-amino-4-deoxy-D-hexuronic acid (the carbohydrate moiety of C-substance) was achieved from methyl 4-azido-4-deoxy-α-D-glucopyranoside (IV, *Figure 2*) which is easily obtained from the readily-available methyl α-D-galactopyranoside (I) by slight modification of the procedure of Reist *et al.*[7]. Selective benzoylation of I afforded the 2,3,6-tri-*O*-benzoate (II) which was mesylated to III and treated with sodium azide in hexamethylphosphorotriamide and then saponified with sodium ethoxide to methyl 4-azido-4-deoxy-α-D-glucoside. Attempts to oxidize IV selectively to the 4-azido-hexuronic acid with platinum catalyst under a variety of conditions were unsuccessful.

However, tritylation of IV afforded the 6-tritylate (V) which was benzoylated and detritylated to methyl 4-azido-4-deoxy-2,3-di-*O*-benzoyl-α-D-glucopyranoside (VI) in which only the 6-hydroxyl is available for oxidation. Oxidation of VI with permanganate in a mixture of acetic acid and acetone followed by esterification with diazomethane afforded the methyl ester (VII) in good overall yield. Debenzoylation of VII with methoxide to VIII followed by reduction over palladium-charcoal afforded the 4-amino derivative (IX) which, after saponification, gave the desired methyl 4-amino-4-deoxy-α-D-glucopyranosiduronic acid (X)[6]. The n.m.r. parameters of the tribenzoylated derivative of IX established the axial orientation for H-2, H-3, H-4 and H-5 and the equatorial orientation for the anomeric proton consistent with the

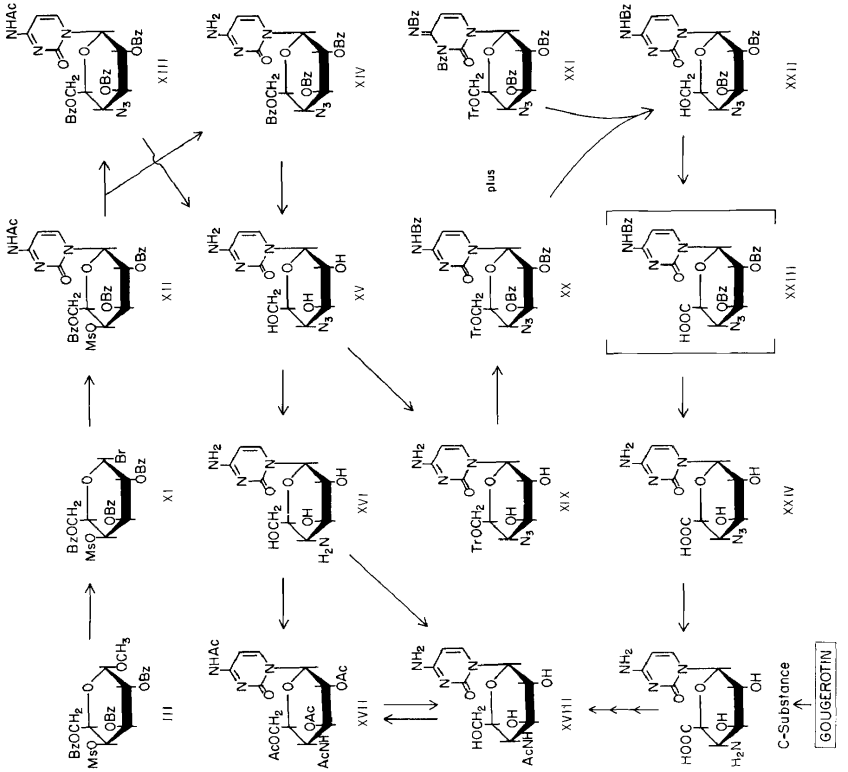

Figure 3

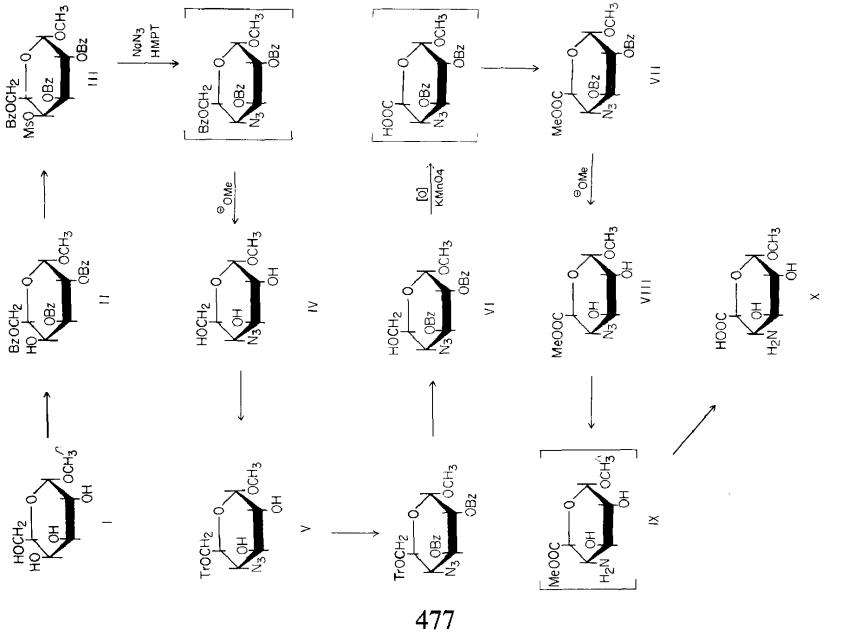

Figure 2

D-*gluco* configuration in the *C1* conformation. It should be noted that compounds VIII and X were the *sole* products obtained even though strongly basic conditions were employed in this reaction sequence, that is, no epimerization at C-5 to the β-L-*ido* configuration was observed.

A practical synthesis of 4′-amino-4′-deoxyglucosyl nucleosides was achieved[8] from the methyl tri-*O*-benzoyl-4-*O*-mesyl-α-D-galactopyranoside (III, *Figure 3*). Treatment of III with HBr-glacial acetic acid at room temperature afforded the α-halogenose (XI, $J_{1,2} = 4.0$ Hz) in high yield. Condensation of XI with N^4-acetylcytosine by the general nitromethane-$Hg(CN)_2$ procedure[9] gave the blocked β-nucleoside (XII, $J_{1',2'} = 9.0$ Hz) in nearly quantitative yield. Reaction of XII with sodium azide in hexamethylphosphoric triamide afforded the crystalline 4′-azido derivatives (XIII and XIV) in high yields. The latter nucleosides were saponified with methoxide to XV and hydrogenated over palladium-charcoal to 1-(4-amino-4-deoxy-β-D-glucopyranosyl)cytosine (XVI). Peracylation or selective *N*-acetylation of XVI afforded nucleosides XVII or XVIII respectively. C-substance (obtained from Gougerotin) was converted in three steps according to Iwasaki[10] into 1-(4-acetamido-4-deoxy-β-D-glucopyranosyl)cytosine (XVIII) and then peracylated to XVII. The nucleosides thus obtained were identical in all respects with synthetic compounds XVII and XVIII obtained from III.

A logical approach to the synthesis of C-substance is either to condense a derivative of 4-amino-4-deoxy-D-glucuronic acid with an appropriate cytosine derivative or to oxidize selectively the 6′-position of nucleosides related to XVI. Attempts to prepare the necessary halogenose from the blocked 4-azido-glucopyranosiduronate (VII, *Figure 2*) were unsuccessful due to the relative instability of the azido group to hydrogen bromide. Platinum-catalysed oxidation of the hydroxymethyl function of several unblocked nucleosides[11] (e.g. 1-β-D-arabinofuranosylcytosine) to the corresponding uronic acid had been reported[11b]; however, nucleosides XV or XVIII were resistant to this procedure. With ruthenium tetroxide, some reaction did occur; however, no product with a cytidine- or uridine-like ultra-violet absorption spectrum could be obtained. Oxidation of XV or XVIII with chromic anhydride-pyridine complex, a method which had been applied successfully to the oxidation of 2′-deoxycytidine to its corresponding uronic acid[12], also failed: the reaction was accompanied by loss of selective absorption in the ultra-violet. Because of these failures we undertook the synthesis of a nucleoside in which only the 6′-hydroxy group is unprotected.

Selective tritylation of XV afforded the 6′-tritylate (XIX) which was benzoylated to a mixture of blocked nucleosides (XX and XXI) and then detritylated to XXII in ethanol-chloroform containing a catalytic amount of hydrochloric acid. Attempts to oxidize XXII with chromic anhydride using a variety of conditions were unsuccessful. It was found, however, that the desired oxidation of XXII proceeded smoothly when it was treated with chromic anhydride in a 1:1 mixture of pyridine-acetic acid containing a small amount of water†. The uronic acid derivative (XXIII) thus obtained

† This reagent mixture [chromic anhydride in pyridine-HOAc(1:1) containing a small amount of water] should find wide usage in the chromic anhydride oxidations of carbohydrates under mild conditions.

was isolated as an amorphous powder, and without further purification was debenzoylated with sodium methoxide to afford a 55 per cent yield (from XXII) of the crystalline 4′-azido-uronic acid derivative (XXIV). Hydrogenation of XXIV over palladium on charcoal gave C-substance in quantitative yield. The crystalline C-substance thus obtained was identical in all respects (u.v., i.r., $[\alpha]_D$ and paper electrophoresis) with that derived by acid hydrolysis of Gougerotin.

The total synthesis of C-substance[8] (*Figure 3*) offered conclusive proof of the structure which we had assigned to it, namely 1-(4-amino-4-deoxy-β-D-glucopyranosyluronic acid)cytosine[13] and constitutes the first synthesis of an aminohexuronic acid nucleoside. The stage is now set for the total synthesis of Gougerotin itself as well as analogues thereof. We are currently heavily engaged in this area and some preliminary studies will be discussed at the conclusion of this lecture. We turn now to our studies directed towards the synthesis of cytosinine, the nucleoside moiety of Blasticidin S.

Cytosinine, the hydrolysis product of Blasticidin S (*Figure 1*), is a nucleoside which contains a new type of carbohydrate, namely a 2,3-unsaturated-4-amino-uronic acid. Our immediate goal was the synthesis of this carbohydrate fragment and a study of its chemical and physical properties[14].

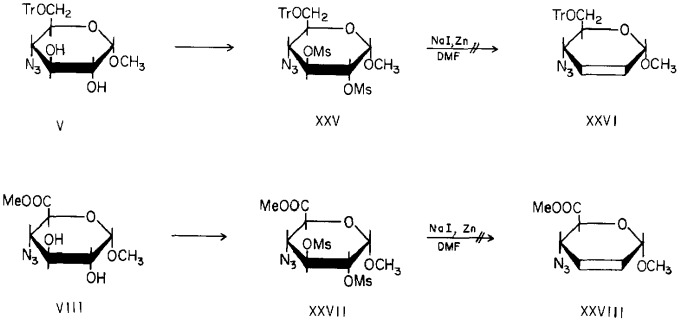

Figure 4

A most direct approach (*Figure 4*) to 2,3-unsaturated-4-amino sugars (XXVI or XXVIII) would be by application of the Tipson-Cohen[15] reaction to suitable 2,3-di-*O*-mesylglucopyranosides (XXV or XXVII), the latter of which were prepared in excellent yield by mesylation of the known (*Figure 2*) precursors V and VIII. However, attempts to convert these dimesylates into the 2,3-unsaturated derivatives by reaction with sodium iodide and zinc gave intractable mixtures. An alternate approach by the epoxide procedure (*Figure 5*) was attempted from the easily obtainable anomers of methyl 3,4-*O*-isopropylidene-D-galactopyranoside (XXIX) each of which was converted to the 3,4-dimesylates (XXX). However, attempts to displace the 4-mesylate by azide ion to give compound XXXI [and thence to the 'down' oxide (XXXII)] failed due to the unexpected inertness of the 4-*O*-mesyl substituent toward substitution by this nucleophile. Compound XXX was recovered unchanged even under conditions (NaN_3 in hexamethylphosphoro-

triamide at 100°) more vigorous than those by which the 4-mesylate of III (*Figure 2*) or by which methyl 6-*O*-benzoyl-tri-*O*-mesyl-α-D-galactoside[16] were converted into their corresponding 4-azido-*gluco* derivatives.

The extremely low reactivity of the 4-mesyloxy substituent of XXX was shown (in the *beta* series) by treatment of XXX with sodium methoxide in methanol at room temperature. Under these conditions the debenzoylated derivative (XXXIII) was obtained which could be re-esterified to XXX. Under more vigorous conditions using a large excess of methoxide and prolonged refluxing, a reaction did occur from which the 3,6-anhydro-4-*O*-mesyl-β-D-galactoside XXXV was the only isolable product (the structure of this product was determined by analysis of its n.m.r. spectrum as well as that of its monoacetate). The intermediary formation of the 2,3-down oxide (XXXIV) was observed during this reaction. A satisfactory explanation of

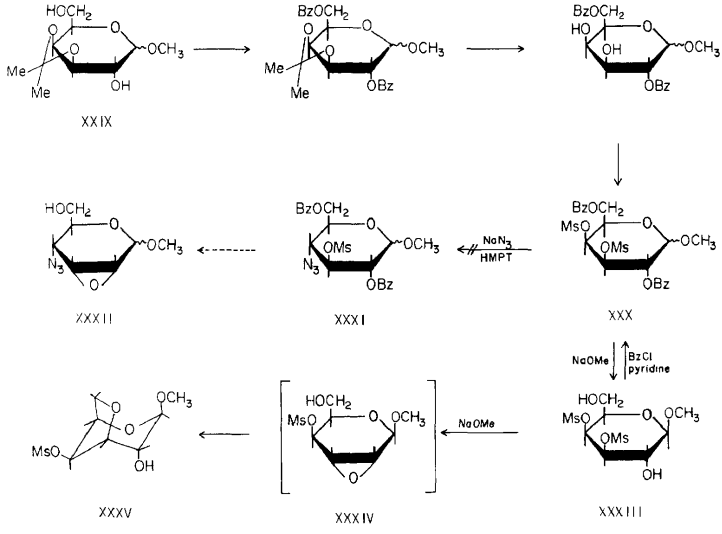

Figure 5

the unexpectedly low susceptibility of the 4-mesylate of XXX to displacement by nucleophiles is yet to be offered. This approach to epoxide XXXII from XXIX (*Figure 5*) was therefore abandoned.

A successful synthesis of methyl 4-amino-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (XLIV, *Figure 6*) was accomplished from V[14]. Selective mesylation of V afforded the crystalline monomesylate (XXXVI) in ~ 60 per cent yield. [The site of mesylation at position 2 was deduced from its n.m.r. spectrum (lower field quartet, $\delta = 4.54$; $J_{1,2} = 3.7$; $J_{2,3} = 9.0$ Hz)]. Treatment of XXXVI with methoxide gave the 'up' oxide (XXXVII) which was detritylated to XXXVIII and converted to its monobenzoate (XXXIX). Reaction of the latter epoxide with sodium iodide by the procedure of Lemieux *et al.*[17] afforded the crystalline iodohydrin XL in almost quantitative yield. [The expected *altro* configuration (diaxial opening) for this iodohydrin was confirmed by an n.m.r. study of its monoacetyl derivative.]

Mesylation of this iodohydrin in pyridine at 4° afforded the monomesylate (XLI). When the reaction was carried out at reflux temperature for 5 minutes, XL was converted directly (via XLI) into the olefin (XLII). Selective reduction

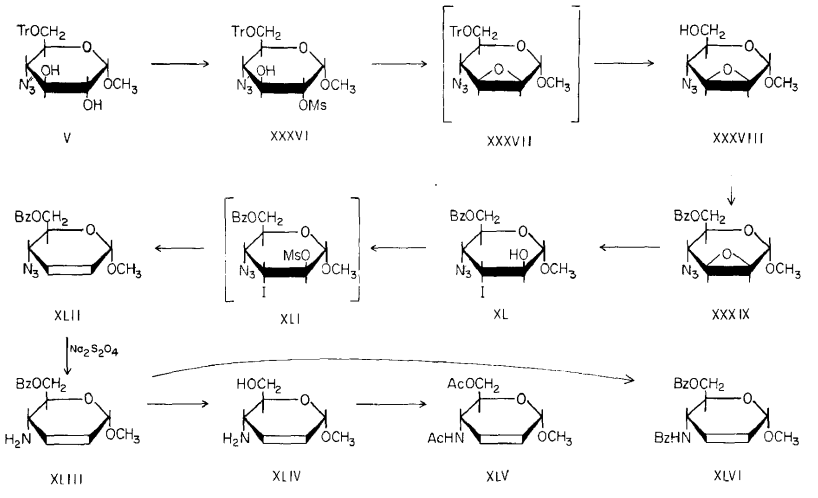

Figure 6

of the azido group to XLIII was achieved with sodium dithionite[18] in acetate buffer and, after debenzoylation with sodium methoxide, afforded the desired 2,3-unsaturated-4-amino sugar (XLIV) as a pure syrup[14]. The syrupy diacetate (XLV) and the crystalline dibenzoate (XLVI) were also prepared.

Attempts to obtain methyl 4-amino-2,3,4-trideoxy-β-D-*erythro*-hex-2-

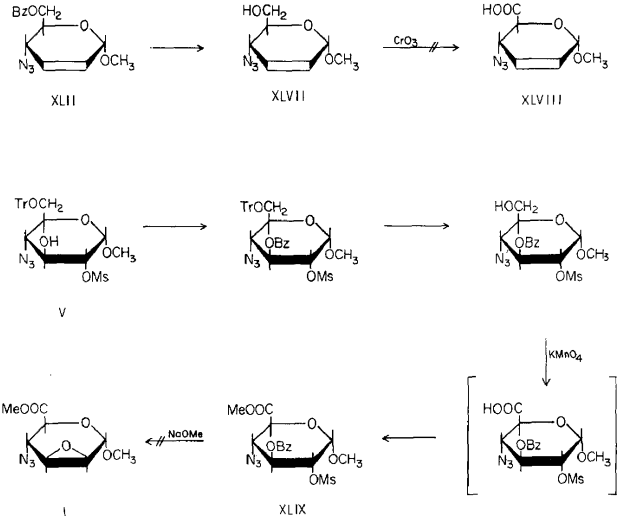

Figure 7

enopyranosiduronic acid (XLVIII, *Figure 7*) from XLII were unsuccessful. Oxidation of XLVII (obtained by debenzoylation of XLII) with chromic anhydride gave an intractable mixture of decomposition products, due probably to the susceptibility of the double bond to the oxidizing agent. It was evident from these studies that conversion to the uronate should precede the formation of the 2,3-double bond. Towards this end, the 6-trityl-4-azido-3-mesylate derivative (V) was benzoylated, detritylated, then oxidized to the uronate and esterified to the 4-azido-2-*O*-mesyl-uronate ester (XLIX). However, attempts to convert this derivative to the 'up' oxide (L) with sodium methoxide led to excessive decomposition and intractable mixtures. These results were unfortunate for they bear on problems related to the total synthesis of cytosinine and suggest that the conversion of the methyl ester of C-substance (*Figure 3*) into cytosinine via a 2,3-epoxide route might not be a fruitful approach. We therefore investigated the direct oxidation of the hydroxymethyl function of preformed 2,3-epoxides (*Figure 8*)[14].

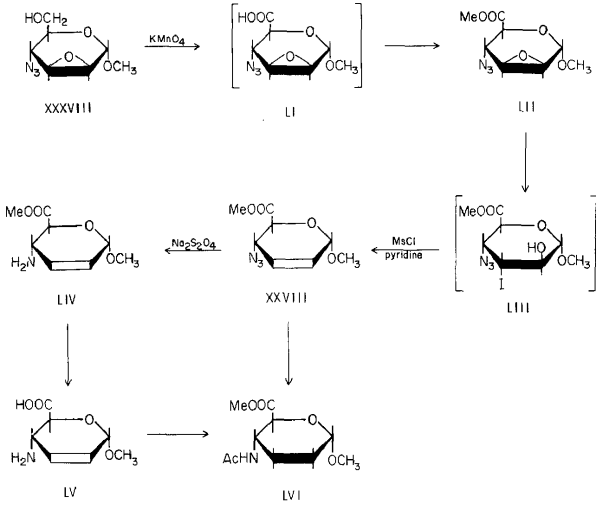

Figure 8

The 4-azido-2,3-*manno* epoxide (XXXVIII) has been obtained previously via the selective mesylation of the 2′-hydroxyl of V. Direct oxidation of XXXVIII with permanganate gave the uronic acid which was esterified with diazomethane to the ester (LII). Treatment with sodium iodide afforded the crystalline iodohydrin (LIII) which was unstable. (The *altro* configuration of LIII was easily established by an n.m.r. study of its monoacetate derivative). Mesylation of LIII in pyridine yielded directly the hitherto-elusive key intermediate, the 2,3-unsaturated-4-azido-uronate ester (XXVIII) as a pure liquid without isolation of the intermediate 2-*O*-mesylate. Reduction of the 4-azido group of XXVIII with dithionite gave the 4-amino derivative (LIV) which, without purification was saponified to crystalline methyl 4-amino-4-deoxy-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranosiduronic acid

(LV). Both LV and XXVIII were converted to the same tetrahydropyran derivative (LVI).

An alternate procedure (*Figure 9*)[14] has also been developed for the

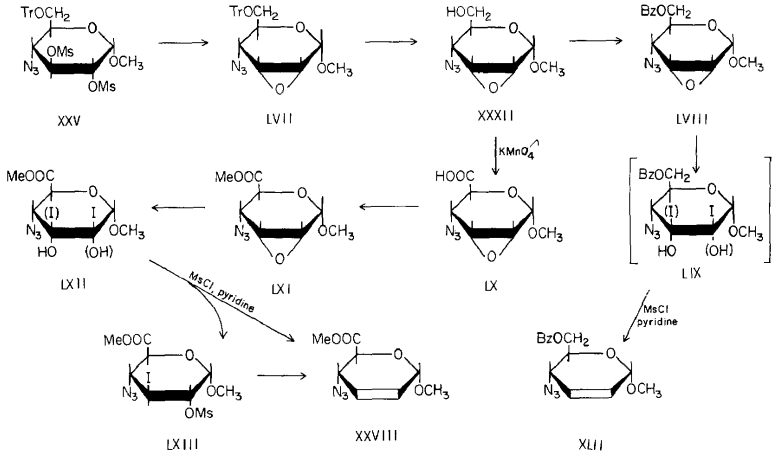

Figure 9

synthesis of the key intermediate (XXVIII) which avoids the lower yielding mesylation step (V → XXVI, *Figure 7*) and which offers the practical advantages of crystalline intermediates and ease of handling. Treatment of XXV, obtained by exhaustive mesylation of V, with sodium methoxide gave the 'down' *allo*-epoxide (LVII) in high yield as the sole product. Detritylation of LVII afforded methyl 2,3-anhydro-4-azido-4-deoxy-α-D-allopyranoside (XXXII) whose structure was established by n.m.r. and by its conversion to the previously-prepared 2,3-unsaturated-4-azido glycoside (XLII) via intermediates LVIII and LIX. Oxidation of epoxide (XXXII) with permanganate to the uronic acid derivative (LX) followed by esterification gave the ester (LXI) which by treatment with sodium iodide afforded a mixture of iodohydrins (LXII). Reaction of this mixture with mesyl chloride in pyridine gave two products which were easily separated. One of these was the unsaturated azido uronate (XXVIII), identical with that obtained by the route described above (*Figure 8*). The other product was the *gluco*-iodohydrin mesylate (LXIII). Compound LXIII was also converted into XXVIII by reaction with tetramethylammonium chloride-zinc dust in pyridine.

The conformation of these new 2,3-unsaturated-4-substituted sugars and uronates was studied[14] by n.m.r. by examination of their $J_{1,2}$, $J_{3,4}$ and $J_{4,5}$ splittings as well as their allylic $J_{2,4}$ couplings. Eight possible conformations were considered (*Figure 10*). The data indicated that those structures which contain the 4-azido function possess the sofa conformation and a similar conclusion was reached[14] for those 2,3-unsaturated-4-aminohexosides in which either the amino and/or the 6-OH was blocked. However with compounds XLIV (*Figure 9*) or LV (*Figure 8*), which contain a free 4-amino group and an unsubstituted 5-hydroxymethyl or -carboxyl function, the

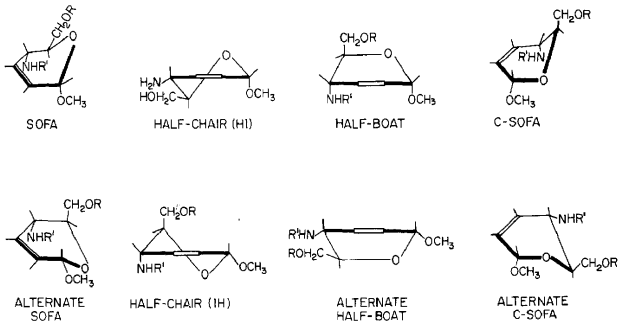

Figure 10

data suggest the half-chair (H1) conformation due probably to intramolecular hydrogen bonding between the 4- and 6-substituents.

Application of these synthetic studies to the synthesis[19] of 2′,3′-unsaturated-4′-aminohexopyranosyl nucleosides (*Figure 11*) utilized the previously prepared[8] 1-(4-azido-4-deoxy-β-D-glucopyranosyl)cytosine (XV, *Figure 3*) an intermediate in our synthesis of C-substance. Selective benzoylation[20] of XV followed by tritylation afforded LXIV which was tosylated, the product refluxed in sodium methoxide in methanol, and then benzoylated with benzoic anhydride in pyridine to LXV. The latter, without isolation, was detritylated to the crystalline 4′-azido-2′,3′-epoxide (LXVI) in 28 per cent overall yield from XV. Acetylation of LXVI followed by treatment of the monoacetate with sodium iodide in acetone gave the crystalline iodohydrin (LXVII). The n.m.r. data for LXVII were consistent with a 3′-iodo derivative of the *altro* configuration which established the *manno* configuration for epoxide LXVI and its crystalline monoacetate derivative and showed, consequently, that monotosylation of LXIV had occurred mainly on position 2′[19].

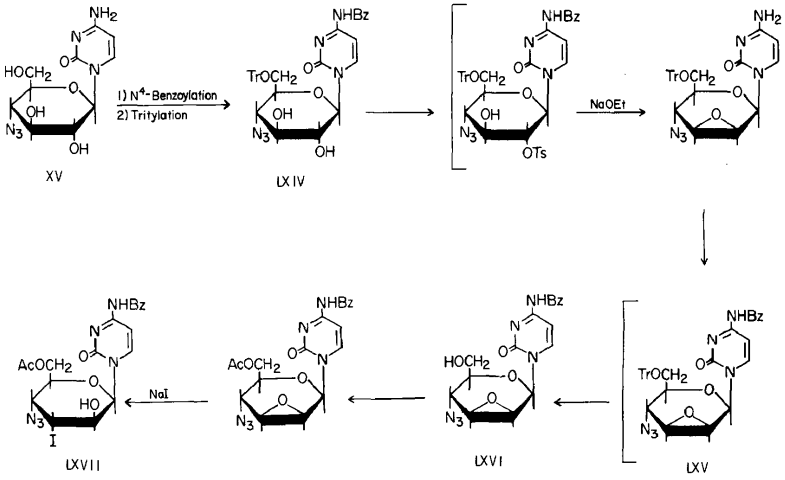

Figure 11

For the introduction of 2′,3′-double bond (*Figure 12*)[19] we made use of experience gained in our above-described studies on the synthesis of 4-substituted-unsaturated sugars. Mesylation of iodohydrin (LXVII) at ~0°

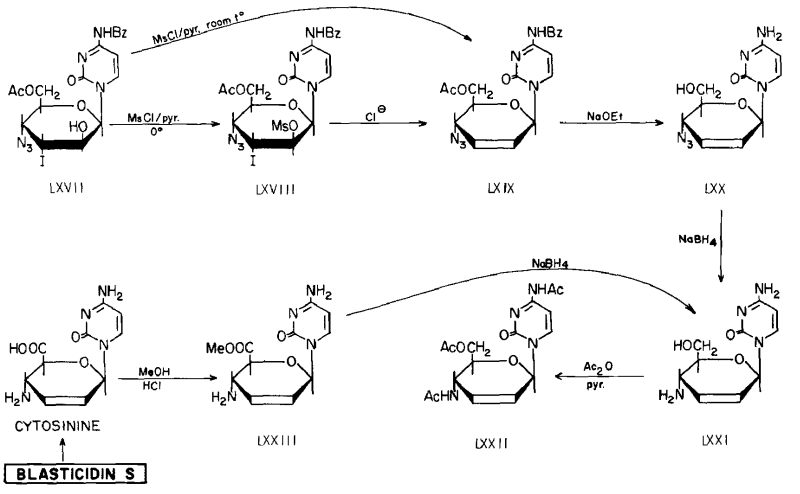

Figure 12

afforded the iodo-mesylate (LXVIII) which was converted easily to the crystalline 2′,3′-unsaturated-4-azido nucleoside (LXIX) by treatment with tetramethylammonium chloride and zinc dust in pyridine. Compound LXIX was obtained directly from the iodohydrin (LXVII) when the mesylation was performed at room temperature. De-acetylation of LXIX with sodium methoxide afforded the crystalline nucleoside (LXX) which after reduction with sodium borohydride gave the 4′-amino-2′,3′-unsaturated nucleoside (LXXI). Acetylation of LXXI yielded LXXII, 1-(4-acetamido-6-*O*-acetyl-2,3,4-trideoxy-β-D-*erythro*-hex-2-enopyranosyl)-N^4-acetylcytosine, in crystalline form.

Yonehara and Ōtake[21] had shown that cytosinine (obtained by hydrolysis of Blasticidin S) could be esterified, reduced with borohydride, and then acetylated to a crystalline diacetyl derivative to which they assigned structure LXXII. Admixture of our synthetic LXXII with a sample† derived from Blasticidin S gave no depression of the melting point. The infra-red spectrum (KBr disc) of our synthetic LXXII was identical with that exhibited by the Blasticidin S-derived material.

It should be noted that the 4′-amino-2′,3′-unsaturated nucleoside differs from cytosinine only by the presence of a hydroxymethyl rather than a carboxyl function on C-5′ and, indeed, the synthesis of LXXI and LXXII constitutes further confirmation of the structure previously assigned[22] to

† We are indebted to Dr Yonehara and Dr Ōtake of the Institute of Applied Microbiology of Tokyo University for this sample.

cytosinine. The total synthesis of cytosinine from suitable chemical precursors described in *Figures 11* or *12* should be feasible.

Our current efforts are devoted primarily toward the total synthesis of Gougerotin and analogues thereof from C-substance† which involve studies on the linkage of suitably protected amino acids or peptides to the 4′-amino group. Several methods of amino-acylation have been attempted using the relatively easily synthesized 4-amino-glycosylcytosine (XVI) as a model. The best results (*Figure 13*) thus far have been obtained with the activated ester[23] approach. As an example, reaction of XVI with the *p*-

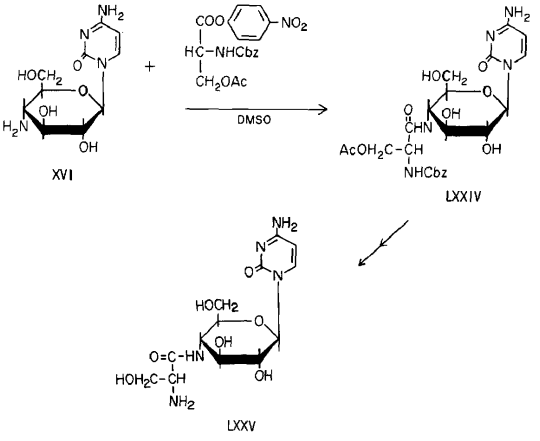

Figure 13

nitrophenyl ester of *N*-carbobenzoxy-*O*-acetyl-D-serine in dimethylsulphoxide at room temperature afforded a good yield of the amino acid-blocked nucleoside (LXXIV)[24]. Removal of the blocking groups was accomplished by treatment of LXXIV with methanolic triethylamine followed by hydrogenolysis in 40 per cent acetic acid to afford crystalline 1-(4-D-serylamido-4-deoxy-β-D-glucopyranosyl)cytosine (LXXV). Application of this reaction to other amino acids, to the ester of C-substance, and to the synthesis of dipeptidyl groups on the 4′-amino group of XVI is under way.

Note added in proof

We have since found that the dicyclohexylcarbodiimide procedure can be used for the linkage of amino acids to XVI. By this procedure 1-[4-deoxy-4-(Sarcosyl-D-seryl)-amino-β-D-glucopyranosyl]cytosine, an analogue of Gougerotin, has been synthesized[24] in good yield and in high optical purity.

† It should be noted that cytosinine may be produced in quantity by hydrolysis of the readily-available Blasticidin S. The fermentation process which produces Gougerotin from *Streptomyces gougerotii* is rather complicated and only very limited amounts of this antibiotic are available. At this time, C-substance, the hydrolysis product of Gougerotin, is best obtained by total synthesis.

ACKNOWLEDGEMENT

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REFERENCES

[1] T. Kanzaki, E. Higashide, H. Yamamoto, M. Shibata, N. Nakazawa, H. Iwasaki, T. Takewaka and A. Miyake, *J. Antibiotics Tokyo* **15A**, 93 (1962).
[2] K. Fukuhara, T. Misato. I. Ishii and M. Asakawa. *Bull. Agr. Chem. Soc. Japan* **19**, 181 (1955); S. Takeuchi, K. Hirayama, K. Ueda, H. Sakai and H. Yonehara. *J. Antibiotics Tokyo* **11A**, 1 (1958).
[3] For general reviews see J. J. Fox, K. A. Watanabe and A. Bloch. *Progr. Nucleic Acid Res. and Mol. Biol.* **6**, 251 (1966); R. J. Suhadolnik, *Nucleoside Antibiotics* John Wiley and Sons, N.Y. (1970).
[4] L. Thiry. *J. Gen. Virol.* **2**, 143 (1968); A. Hirai, S. G. Wildman and T. Hirai. *Virology* **36**, 646 (1968).
[5] T. Misato, I. Ishii, M. Asakawa, Y. Okimoto and K. Fukunaga. *Ann. Phytopathol. Soc. Japan* **24**, 302, 307 (1959).
[6] M. P. Kotick, R. S. Klein, K. A. Watanabe and J. J. Fox, *Carbohydrate Res.* **11**, 369 (1969).
[7] E. J. Reist, R. R. Spencer, D. F. Calkins, B. R. Baker, and L. Goodman, *J. Org. Chem.* **30**, 2312 (1965).
[8] K. A. Watanabe, M. P. Kotick and J. J. Fox. *Chem. Pharm. Bull. Tokyo* **17**, 416 (1969); *idem, J. Org. Chem.* **35**, 231 (1970).
[9] K. A. Watanabe and J. J. Fox. *J. Heterocyclic Chem.* **6**, 109 (1969); N. Yamaoka. K. Aso and K. Matsuda. *J. Org. Chem.* **30**, 149 (1965).
[10] H. Iwasaki. *Yakugaku Zasshi* **82**, 1385 (1962).
[11] (a) G. P. Moss, C. B. Reese, K. Schofield, R. Shapiro and A. R. Todd, *J. Chem. Soc.* 1149 (1963); (b) K. Imai and M. Honjo. *Chem. Pharm. Bull. Tokyo* **13**, 7 (1965); K. C. Tsou, N. J. Santora and E. E. Miller. *J. Med. Chem.* **12**, 173 (1969).
[12] A. S. Jones, A. R. Williamson, and M. Winkley. *Carbohydrate Res.* **1**, 187 (1965)
[13] J. J. Fox, Y. Kuwada and K. A. Watanabe. *Tetrahedron Letters* 6029 (1968).
[14] K. A. Watanabe, R. S. Goody and J. J. Fox. *Tetrahedron* **26**, 3883 (1970); R. S. Goody, K. A. Watanabe and J. J. Fox. *Tetrahedron Letters* 293 (1970).
[15] R. S. Tipson and A. Cohen, *Carbohydrate Res.* **1**, 338 (1965); E. Albano, D. Horton and T. Tsuchiya. *ibid.* **2**, 349 (1966); J. Hildesheim, J. Cléophax and S. D. Gero. *Tetrahedron Letters* 1685 (1967).
[16] K. A. Watanabe and J. J. Fox. Unpublished results.
[17] R. U. Lemieux, E. Fraga and K. A. Watanabe. *Can. J. Chem.* **46**, 61 (1968).
[18] R. Adams and W. Moje. *J. Am. Chem. Soc.* **74**, 5560 (1952).
[19] K. A. Watanabe, I. Wempen and J. J. Fox. *Chem. Pharm. Bull. Tokyo* **18**, 2368 (1970).
[20] K. A. Watanabe and J. J. Fox. *Angew. Chem. Intern. Ed. Engl.* **5**, 579 (1966).
[21] H. Yonehara and N. Ōtake. *Tetrahedron Letters* 3785 (1966).
[22] N. Ōtake, S. Takeuchi, T. Endo and H. Yonehara. *Tetrahedron Letters* 1404, 1411 (1965); *idem., Agr. Biol. Chem. Tokyo*, **30**, 126, 132 (1966); J. J. Fox and K. A. Watanabe. *Tetrahedron Letters* 897 (1966)
[23] M. A. Ondetti. *J. Med. Chem.* **6**, 10 (1963).
[24] K. A. Watanabe, E. A. Falco and J. J. Fox. Submitted for publication.