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NUCLEOSIDES—LXVIII

SYNTHETIC STUDIES ON NUCLEOSIDE ANTIBIOTICS. 5. 4-AMINO-2,3-UNSATURATED SUGARS RELATED TO THE CARBOHYDRATE MOIETY OF BLASTICIDIN S*

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Abstract—Methyl 4-amino-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (**24**) and its crystalline dibenzoate (**26**) were synthesized from methyl 4-azido-4-deoxy-6-*O*-trityl-α-D-glucoside (**1**) by a route involving the 2,3-anhydromannoside derivative (**18**) and the 3-iodo-altroside (**20**). Treatment of **20** with mesyl chloride in pyridine gave the 2-enopyranoside (**22**) which after reduction with sodium dithionite followed by debenzoylation afforded the 2,3-unsaturated-4-amino sugar derivative (**24**), a member of a new class of carbohydrates. An alternate synthesis of the key intermediate (**22**) from methyl 4-azido-4-deoxy-2,3-di-*O*-mesyl-6-*O*-trityl-α-D-glucoside (**2**) was achieved *via* the *allo*-epoxide (**12**).

The synthesis of methyl 4-amino-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranosiduronic acid (**38**), related to the carbohydrate moiety of Blasticidin S, was achieved from **18** by oxidation and esterification to the 2,3-anhydro-4-azido-α-D-mannosiduronate (**33**) which was converted into the 3-iodo-altrosiduronate (**35**) and thence to methyl (methyl 4-azido-2,3,4-trideoxy-α-D-*erythro*-hex-2-enosid)uronate (**6**). Reduction and saponification of **6** afforded crystalline **38**. An improved synthesis of **6** was achieved from **12** *via* the crystalline 2,3-*allo*-epoxides **44** and **45**.

Conformational aspects of these 4-amino-2,3-unsaturated sugars are discussed.

AS PART of our program directed toward the synthesis and biological evaluation of pyrimidine nucleoside antibiotics[1,2] related to Gougerotin[3] (Chart 1) we recently reported the total synthesis of C-substance[4] and of methyl 4-amino-4-deoxy-α-D-glucopyranosiduronic acid,[5] the carbohydrate moiety of this antibiotic. A structurally-related antibiotic, Blasticidin S,[6] is a powerful agent against rice blast disease[7] and is also an inhibitor of tobacco mosaic virus-RNA synthesis.[8] Like Gougerotin, Blasticidin S also inhibits the incorporation of amino acids into protein on the aminoacyl-tRNA ribosomal level.[9] Blasticidin S contains the 1-(4-amino-2,3,4-trideoxy-β-D-*erythro*-hex-2-enopyranosyluronic acid)cytosine [cytosinine, Chart 1] structure.[10]

This paper deals with the first syntheses† of 2,3-unsaturated amino sugars, the

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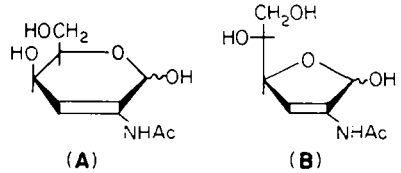
† To our best knowledge only two 2,3-unsaturated amino-sugar derivatives, namely (A)[11a] and (B),[11b] appeared in the literature. The structure of (A) was recently disproved.[11c] The structure (B) was tentatively assigned and is not firmly established. Only a few examples of 2,3-unsaturated carbohydrates containing



(A) (B)

functional groups other than OH (or substituted OH) are known, namely, methyl 3,4-dichloro-2,3,4-trideoxy-D-*glycero*-pent-2-enopyranosides[11d,e] and methyl *glycero*-hex-2-enopyranosid-4-ulose,[11f] methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside[11g] and methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro* (and -*threo*)-hex-2-enopyranosides.[11h]

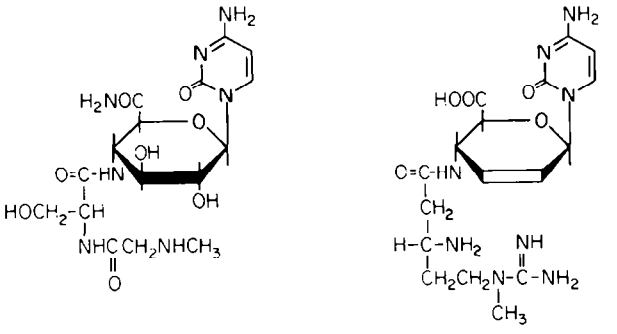


CHART 1

4-amino-2,3,4-trideoxy-D-*erythro*-hex-2-enopyranosides, a new class of carbohydrates. In addition, we report the synthesis of derivatives of 4-amino-2,3,4-trideoxy-D-*erythro*-hex-2-enopyranuronic acid, the carbohydrate moiety of Blasticidin S. A preliminary report has appeared.[12]

The most direct approach to 2,3-unsaturated sugars (**3** or **6**) would be by application of the Tipson-Cohen[13] reaction to the suitable 2,3-di-O-mesylglucopyranosides **2** and **5** (Chart 2). These derivatives were prepared by mesylation of the known[5] precursors **1** and **4**. However, attempts to convert **2** into **3** or **5** into **6** by reaction with sodium iodide and zinc in DMF gave intractable mixtures of many components. An alternate approach by the epoxide procedure[14,15] to give **12** was also attempted starting from the easily obtainable anomers[16] of methyl 3,4-O-isopropylidene-D-galactopyranoside (**7**), each of which was converted (as shown in Chart 2) to the 3,4-di-O-mesylates (**10**). However, attempts to displace the 4-mesylate of **10** by azide ion to give **11** were unsuccessful due to the unexpected* inertness of the 4-O-mesyl substituent toward substitution by this nucleophile. Unchanged **10** was recovered from the attempted reaction with NaN_3 in hexamethylphosphorotriamide even under conditions more vigorous (100°) than those by which methyl tri-O-benzoyl-

* It is known that the 4-mesyloxy group of methyl 2,3,4,6-tetra-O-mesyl-D-glucoside could be replaced by azide while the 2- and 3-mesyloxy groups remain intact.[17a] Recently Dick and Jones[17b,c] successfully replaced only the 4-mesyloxy group of several poly-O-mesyl-D-glycopyranosides by azide. The high reactivity of the 4-mesyloxy group and the relatively low reactivity of the 2- and 3-mesyloxy functions of glycopyranosides were discussed by Hill *et al.*[17d]

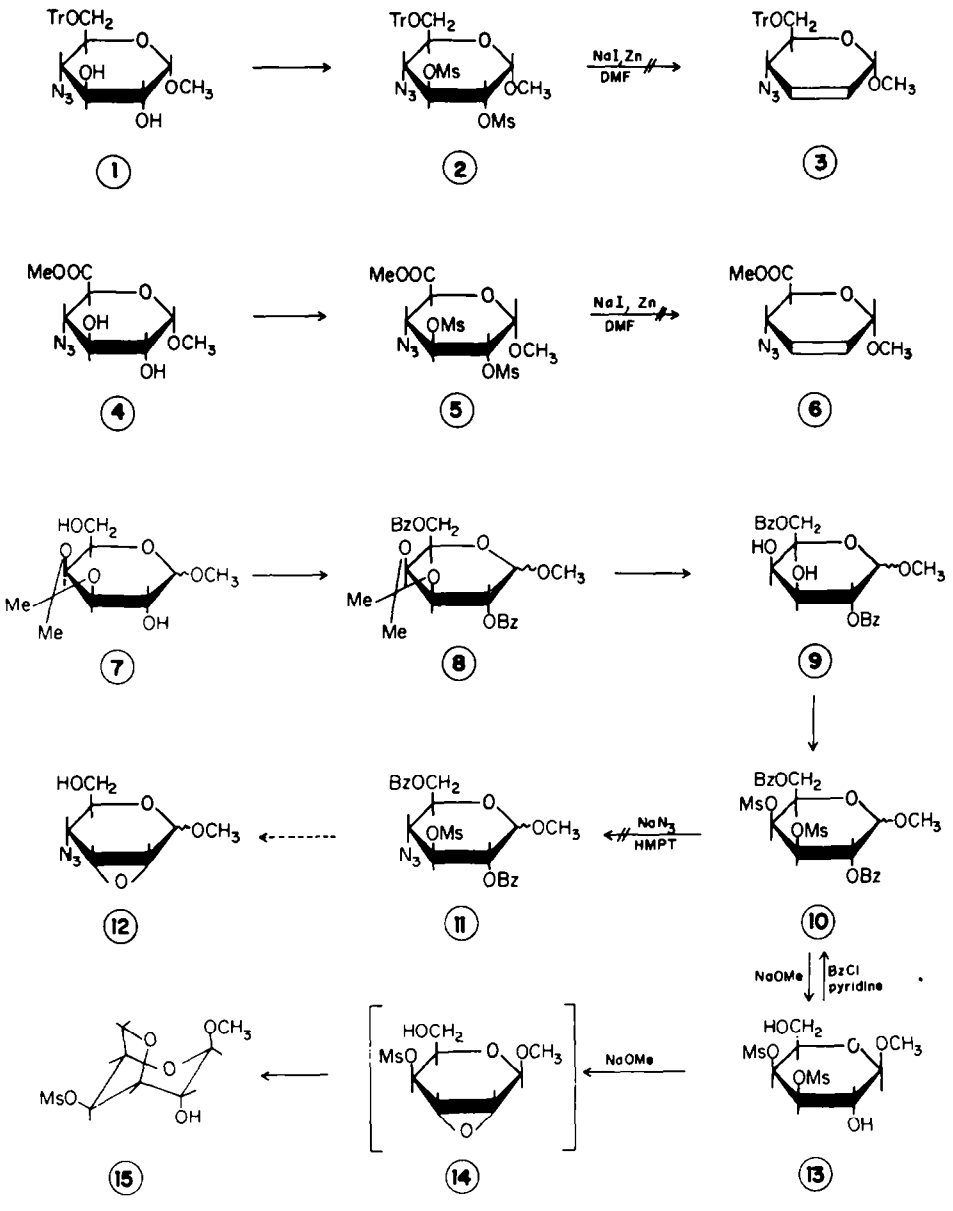


CHART 2

4-O-mesyl-α-D-galactopyranoside[5] or methyl 6-O-benzoyl-tri-O-mesyl-α-D-galactoside[18] were converted into their corresponding 4-azido-*gluco* derivatives. It should be noted that in the *beta* series of **7**–**10**, all intermediates were easily obtained in high yields in crystalline form.

The extremely low reactivity of the 4-mesyloxy group of **10** was shown (in the *beta* series) by treatment of **10** with sodium methoxide in methanol at room temperature.

Under these conditions, the debenzoylated-3,4-dimesylate (**13**) was obtained which could be re-esterified to **10**. Under more vigorous conditions using a large excess of methoxide and prolonged refluxing, a reaction did occur which was monitored by thin layer chromatography (TLC) and showed the intermediary formation of epoxide (**14**). The only isolable product was methyl 3,6-anhydro-4-O-mesyl-β-D-galactoside (**15**). The structure of **15** was established by elemental analyses and from the NMR spectra of **15** and of its monoacetate (Table 1) which showed the presence of one mesyl and one hydroxyl function. The non-equivalence of the C-6 protons establishes the involvement of this position in the anhydro linkage. The large difference between the $J_{5,6}$ and the $J_{5,6'}$ values would support the 3,6-anhydro structure. The formation of 3,6-anhydro-D-galactose from methyl 2,3-anhydro-α-D-gulopyranoside has been reported.[19]

It is conceivable that in the conversion of **8** → **10** benzoyl migration to C-4 had occurred and that compound **10** is actually the 4,6-di-O-benzoyl-2,3-dimesylate. This postulate would account for the resistance of any of its mesyloxy groups to displacement by azide. However, direct mesylation of methyl 4,6-O-benzylidene-β-D-galactopyranoside followed by de-benzylidenation gave methyl 2,3-di-O-mesyl-β-D-galactopyranoside which was *not* identical with **13**. Since **10** was also prepared from **13** it is clear that compound **10** is the 3,4-dimesylate, as depicted in Chart 2. A satisfactory explanation of the unexpected low reactivity of the 4-mesylate of **10** to nucleophiles is yet to be offered. The approach to epoxide **12** from **7** was therefore abandoned.

A successful synthesis of methyl 4-amino-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (**24**) was accomplished from compound **1** as shown in Chart 3. Selective mesylation of **1** afforded the crystalline monomesylate (**16**). The lower field quartet in the NMR spectrum of **16** (δ = 4·54, $J_{1,2}$ = 3·7; $J_{2,3}$ = 9·0 Hz) established the site of mesylation at position 2. Treatment of **16** with sodium methoxide gave the epoxide **17** which was detritylated to **18** which, without purification, was converted to the monobenzoate (**19**). The NMR parameters of **17** and **19** (Table 2) are in good agreement with those reported for 2,3-epoxides of the *manno* configuration.* Reaction of **19** with sodium iodide by the reported procedure[15] afforded the crystalline iodohydrin (**20**) in almost quantitative yield. The expected *altro* configuration for **20** (diaxial opening) was confirmed by an NMR study of its acetate derivative. The low field narrow quartet at δ = 5·27 ($J_{1,2}$ = 3·0; $J_{2,3}$ = 1·0 Hz) excluded the isomeric *gluco* structure. Treatment of **20** with mesyl chloride in pyridine[15] at reflux temperature for 5 min gave a near-quantitative yield of olefin (**22**). When the reaction was carried out at 4°, the formation of iodomesylate (**21**) was detected by TLC along with olefin (**22**). Attempts to reduce the azido group of **22** with sodium borohydride failed although Stevens *et al.*[21] and Ali and Richardson[22] reported on the ease of reduction of azides to amines by this reagent. At 0°, no reaction occurred while at higher temperatures the benzoyl function was reduced to benzyl alcohol prior to reduction of the azido group. Selective reduction of the azido group to compound **23** was achieved with sodium dithionite[23] in acetate buffer. During the reduction O → N benzoyl migration occurred to a small extent as had been observed previously[5] during the hydrogenation of methyl 4-azido-4-deoxy-tri-O-benzoyl-α-D-glucopyranoside.

* It was reported[20] that the coupling between the epoxide ring protons and the adjacent protons were smaller when these atoms had a *trans* (rather than *cis*) relationship so that in the α-*allo* ("down" epoxide) structure $J_{1,2} \cong J_{3,4}$ = 2·5–4·5 Hz while the α-*manno* epoxides $J_{1,2} \cong J_{3,4} = 0$.

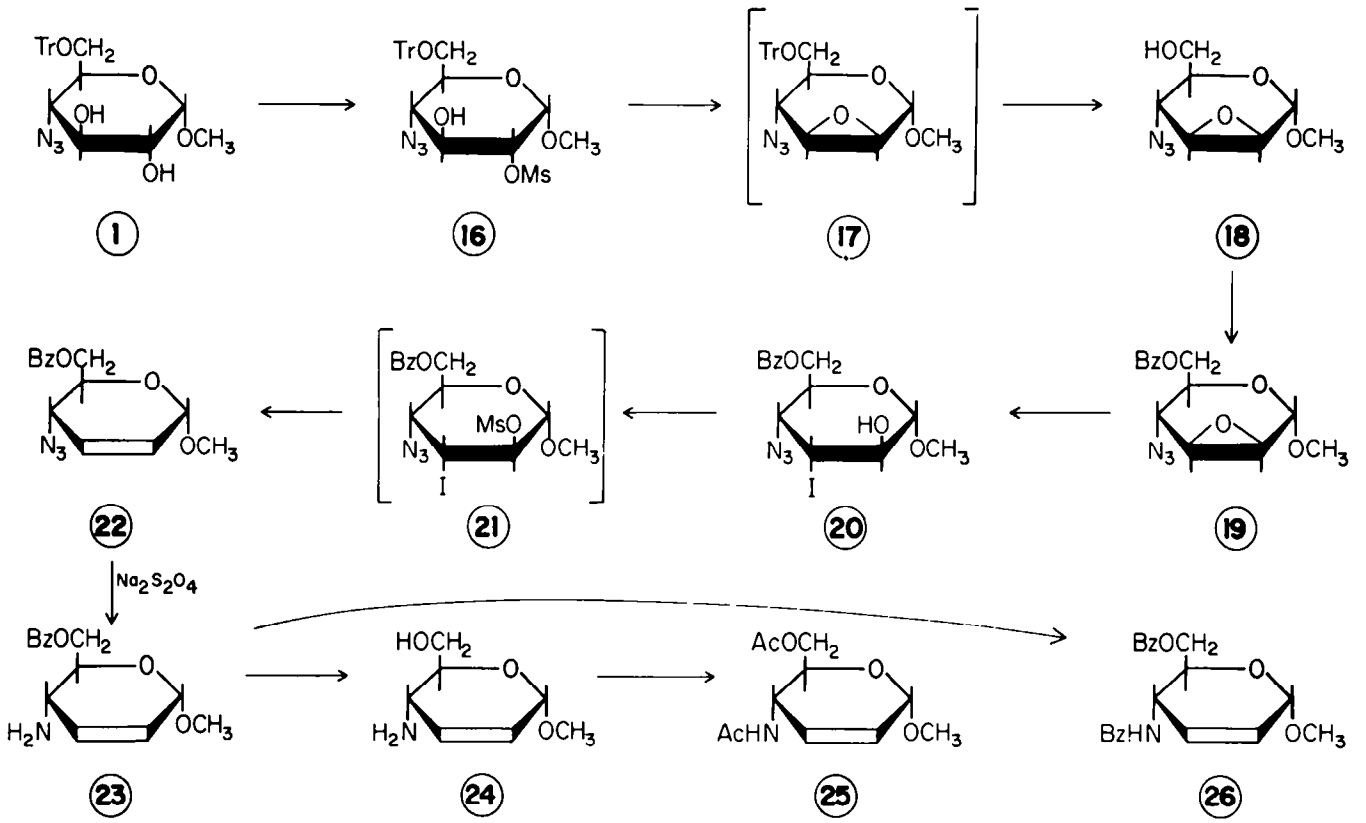

TrOCH2
OH
N3
OCH3
OH
1
TrOCH2
OH
N3
OCH3
OMs
16
TrOCH2
O
N3
OCH3
17
HOCH2
O
N3
OCH3
18
BzOCH2
O
N3
OCH3
19
BzOCH2
HO
N3
OCH3
I
20
BzOCH2
MsO
N3
OCH3
I
21
BzOCH2
N3
OCH3
22
Na2S2O4
BzOCH2
H2N
OCH3
23
HOCH2
H2N
OCH3
24
AcOCH2
AcHN
OCH3
25
BzOCH2
BzHN
OCH3
26

CHART 3

Benzoylation of the O- and N-benzoates afforded the crystalline dibenzoate derivative (**26**). Debenzoylation of **23** with sodium methoxide gave the desired 2,3-unsaturated-4-amino sugar (**24**) as a pure syrup which gave a syrupy diacetate (**25**).

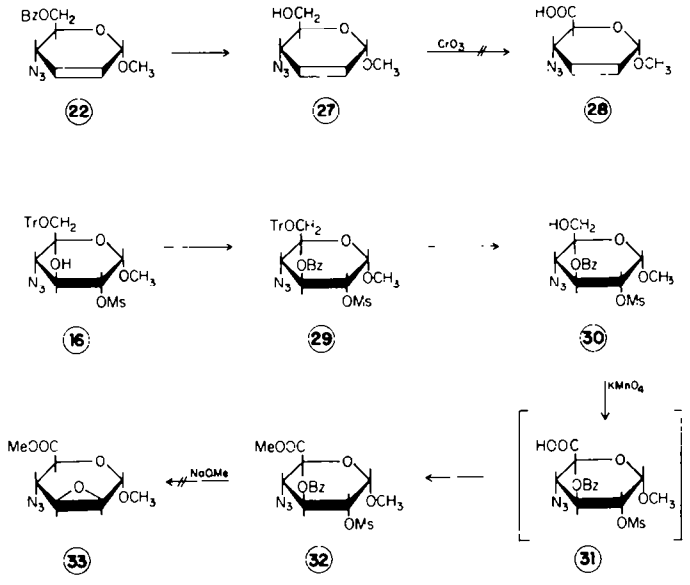
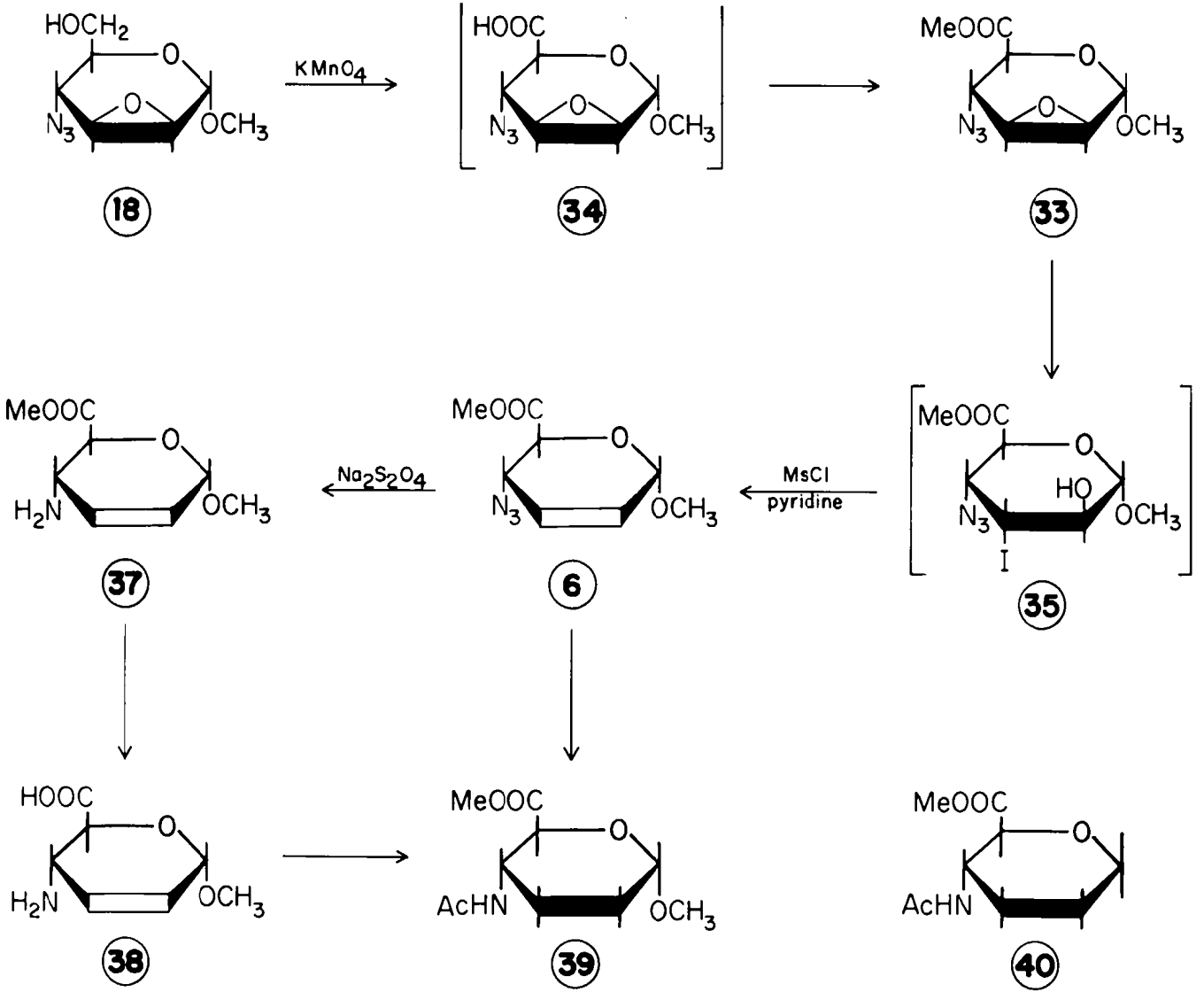


CHART 4

Attempts to obtain methyl 4-amino-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranosiduronic acid (the carbohydrate moiety of Blasticidin S) from **22** were unsuccessful (Chart 4). Oxidation of **27**, obtained by debenzoylation of **22**, with chromic anhydride[4] did not give **28** but rather an intractable mixture of decomposition products. A 4-azido uronate (**32**) was synthesized from compound **16** by benzoylation followed by detritylation to **30**. Permanganate oxidation[5,24] of **30** afforded the uronic acid **31** which was esterified to **32** (isolated as a pure syrup). However attempts to convert **32** with sodium methoxide in methanol to epoxide (**33**) was accompanied by excessive decomposition and led to intractable mixtures. These studies indicate that it will be difficult if not impossible to obtain 2,3-epoxides from uronate esters.* We therefore investigated the direct oxidation of the hydroxymethyl function of epoxide derivatives (Chart 5).

Permanganate oxidation of epoxide **18** gave the uronic acid derivative (**34**) which without purification, was esterified with diazomethane to **33** in ~30% overall yield from **18**. Treatment of **33** with NaI gave the crystalline iodohydrin (**35**) which was unstable and was difficult to isolate in a pure state. The *altro* configuration for **35** was easily established by an NMR study of its acetate (low field narrow quartet at $\delta = 5{\cdot}25$, $J_{1,2} = 4{\cdot}0$; $J_{2,3} = 6{\cdot}2$ Hz). Treatment of **35** with mesyl chloride in pyridine

* These results have bearing on problems related to the total synthesis of cytosinine (Chart 1). They suggest that the conversion of the methyl ester of C-substance into cytosinine by the 2,3-epoxide route may not be successful.


HOCH2
O
O
N3
OCH3
18
KMnO4
HOOC
34
MeOOC
33
MeOOC
HO
I
35
MsCl
pyridine
Na2S2O4
H2N
37
6
HOOC
38
AcHN
39
40

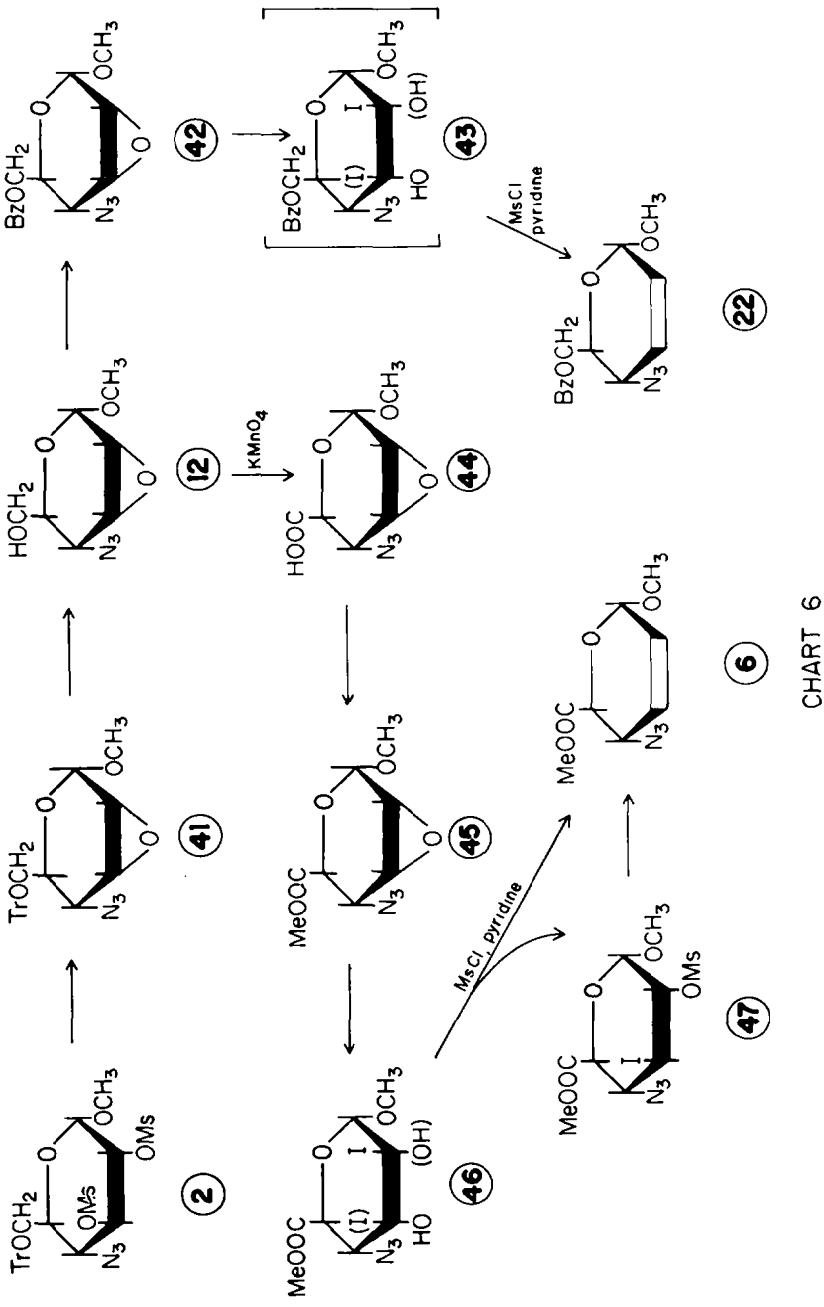

TrOCH2
OMs
OCH3
OMs
N3
2
TrOCH2
OCH3
N3
41
HOCH2
OCH3
N3
12
KMnO4
HOOC
OCH3
N3
44
BzOCH2
OCH3
N3
42
BzOCH2
OCH3
I
(I)
N3
HO
(OH)
43
MsCl
pyridine
BzOCH2
OCH3
N3
22
MeOOC
OCH3
N3
45
MeOOC
OCH3
I
(I)
N3
HO
(OH)
46
MsCl pyridine
MeOOC
OCH3
N3
6
MeOOC
OCH3
I
N3
OMs
47

CHART 6

afforded [without isolation of the intermediate 2-O-mesylate (**36**)] the unsaturated derivative (**6**) which was obtained as a pure liquid. Reduction of the azido function with sodium dithionite at pH 7 yielded compound **37** which, without purification, was de-esterified to crystalline methyl 4-amino-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranosiduronic acid (**38**).

Hydrogenation of **38** in the presence of platinum catalyst followed by acetylation with acetic anhydride in methanol and then esterification with diazomethane afforded crystalline methyl (methyl 4-acetamido-2,3,4-trideoxy-α-D-*erythro*-hexopyranosiduronate) (**39**). This compound was also obtained by reduction of **6** followed by acetylation. The compound, (2S)-methoxycarbonyl-(3S)-acetamido-tetrahydropyran (**40**), which had been isolated as a hydrogenolysis product from cytosinine by Otake *et al.*,[10] was not detected in the reaction mixture.

A procedure for the preparation of the key intermediate (**6**) via the "down oxide" route which avoids the low-yielding selective mesylation step (**1** → **16**) and which offers practical advantages (crystalline intermediates and ease of handling) is given in Chart 6. Treatment of **2** with sodium methoxide gave the *allo*-epoxide **41** in high yield as the sole product as evidenced by TLC. [It should be noted that in many other cases[17b,c] 2,3-dimesylates of 4-azido sugars gave mixtures of "up" and "down" epoxides]. Detritylation of **41** afforded methyl 2,3-anhydro-4-azido-4-deoxy-α-D-allopyranoside (**12**) whose structure was established by NMR (see Table 2) and by its conversion to the 2,3-unsaturated azido sugar (**22**) *via* intermediates **42** and **43**. Oxidation of **12** to the uronic acid derivative (**44**) followed by esterification gave the ester (**45**) which by treatment with sodium iodide gave a mixture of iodohydrins (**46**). Reaction of the latter mixture in mesyl chloride in pyridine gave two products which were easily separated by column chromatography. One of these was the unsaturated azido sugar (**6**), identical with that obtained from **18**, and the other was the *gluco*-iodohydrin mesylate (**47**). The latter compound was also converted into **6** by reaction with tetramethylammonium chloride–zinc dust in pyridine.[25]

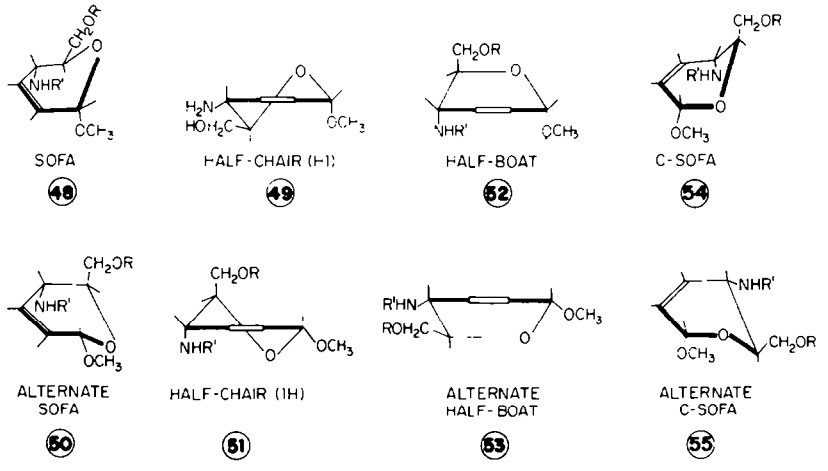


CHART 7

The structure and conformation of this new class of unsaturated amino sugars were established by NMR studies (Table 3). The low field signals ($\delta \sim 5{\cdot}9$, integrated for 2 protons) were easily assigned to vinylic (H2 and H3) resonances, of which H2 (and hence H3) were assigned on the basis of H1–H2 coupling observed in the anomeric signal. In the half-chair conformation **49** (which is most favored for unsaturated cyclic 6-membered ring systems)[26] or in the sofa conformation* (**48**, Chart 7) the dihedral angle between H1 and H2 is in the $\sim$30–45° range while that for H3 and H4 is $\sim$60–90°. It is to be expected therefore that the couplings between H3 and H4 would be smaller than those between H1 and H2. Experimentally we find $J_{1,2} \sim 2$ and $J_{3,4} \sim$ zero which are consistent with these conformations.†

The anomeric and two H6 signals were assigned on the basis of their chemical shifts and the shapes of their resonance signals. The assignments for the signals of H4 and H5 were derived from the fact that the H4 signals of both anomers of methyl 4-acetamido-triO-acetyl-4-deoxy-D-glucopyranoside occurred at lower field than did H5,[3b,32] and the chemical shift of H5 should be affected less by the change of substituent at C4 than H4.

The above data establish the location of the unsubstituted double bond. The large coupling constant for H4 and H5 establish the *trans* axial-*quasi*-axial relationship between these two protons. This relationship is important since it was found that tetra-O-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranose rearranged slowly to the corresponding α-D-*threo* enantiomer by epimerization of the allylic 4-acetoxy group.[33]

It is interesting to note that (except for compound **24**) the allylic coupling ($J_{2,4}$) is very small for the amino-unsaturated sugars (Table 3). If these compounds take the half-chair conformation, the dihedral angle between H3 (hence H2) and H4 is approximately 90° and $J_{2,4}$ should be $\sim$2 Hz according to Garbisch's relationship.[29] He showed that the magnitude of allylic coupling is dihedral angle-dependent and may be represented by:

$$^4J = 1{\cdot}3\cos^2\phi - 2{\cdot}6\sin^2\phi \; (0° \leqq \phi \leqq 90°)$$
$$^4J = -2{\cdot}6\sin^2\phi \; (90° \leqq \phi \leqq 180°)$$

where ϕ is the dihedral angle between the vinyl and allylic C—H bonds. Therefore, the very small allylic coupling ($\sim$0) found in these compounds indicates that their

* The term "sofa" is adopted from Philbin and Wheeler.[27a] The terminology for the conformation of cyclohexenes is rather confused. In some cases "boat" is used for "half-boat"[27b] and "half-boat" is used for "sofa". We use herein conformational terms ("half-chair" and "half-boat") to conform to those generally seen in text books.[28]

† The Karplus relationship cannot be applied to protons attached to sp^2 carbons. The proposed equation for vinyl-allylic couplings[29]

$$^3J = 6{\cdot}6\cos^2\phi + 2{\cdot}6\sin^2\phi \; (0° \leqq \phi \leqq 90°)$$

is not applicable to compounds listed in Table 3 because the minimum $J_{3,4}$ value predicted by this equation is 2·6 while those for compounds in Table 3 show much smaller values for $J_{3,4}$. The inapplicability of the above equation to an unsaturated carbohydrate has also been demonstrated.[30] The vinyl-allylic couplings have been shown[31] to be dependent upon the angle which the allylic proton makes with the olefinic plane. It is therefore safe to state that as the dihedral angle approaches 90°, the ^3J vinyl-allylic couplings approach zero.

TABLE 1. NMR PARAMETERS OF *O*-MESYL DERIVATIVES

Compound	Chemical shift (δ)								Approx J value (Hz)				Solvent
	H1	H2	H3	H4	H5	H6, 6′	OCH_3	SCH_3	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	
2	5·15	5·07	4·70	4·17			3·37	3·37, 3·28	3·0	9·0	9·0		DMSO-d_6
5		5·34					3·48	3·48, 3·40	2·0	9·3			C_5D_5N
10β	4·67	5·57	5·12	5·93	4·27	5·67	3·50	3·17, 2·90	8·0	10·0	3·0		$CDCl_3$
13β	4·42		4·82	5·18			3·52	3·26	8·0	10·0	3·5		Acetone-d_6
15	4·41	3·90	4·32	5·16	4·57	*a*	3·28	3·28	0	5·0	0	1·8	DMSO-d_6
15(Ac)	4·52	4·83	4·46	5·03	4·65	*b*	3·31	3·31	0	5·0	0	2·0	DMSO-d_6
16	5·02	4·53		4·03			3·38	3·10	3·5	9·0			$CDCl_3$
29	5·17	5·05	5·55	4·19			3·41	3·17	3·5	9·5	9·5	9·5	DMSO-d_6
30	5·11	4·94	5·58	4·13	3·83	4·42	3·42	3·13	3·5	9·5	9·0	9·5	DMSO-d_6
32	5·18	5·02	5·54	4·38	4·17		3·48	3·14	3·0	9·5	9·5	10·0	DMSO-d_6
47	4·94	4·71					3·51	3·22	3·5	10·0			$CDCl_3$

[a] $\delta_{H6} = 4·10$, $\delta_{H6'} = 3·72$, $J_{5,6} = 0$, $J_{5,6'} = 3·0$, $J_{6,6'} = -10·0$. [b] $\delta_{H6} = 4·18$, $\delta_{H6'} = 3·81$, $J_{5,6} = 0$, $J_{5,6'} = 3·0$, $J_{6,6'} = -10·0$ (the negative sign is assumed).

TABLE 2. NMR PARAMETERS OF 2,3-ANHYDRO SUGAR DERIVATIVES

Compound	Chemical shift (δ)							Approx J value (Hz)				Solvent
	H1	H2	H3	H4	H5	H6, 6′	OCH_3	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	
12	4·93						3·32	2·8				DMSO-d_6
17	4·97	3·08	3·33	3·67	3·67	3·30	3·52	0	4·0	0		$CDCl_3$
19	4·92	3·13	3·41	3·7–3·9		4·48	3·45	0	3·7	0		$CDCl_3$
35	5·03	3·14	3·38	4·07	4·07		3·56	0	3·7	0		$CDCl_3$
40	4·97	3·43	3·78	3·18	3·97	3·49		2·3	4·0	4·0	10·0	$CDCl_3$
41	4·96	3·75–3·45		4·11	~3·6	4·52	3·47	3·0				$CDCl_3$
43	5·03			3·78	4·37		3·51	2·5			9·5	$CDCl_3$
44	5·00			3·85	4·30		3·49	2·5			9·5	$CDCl_3$

TABLE 3. NMR PARAMETERS OF UNSATURATED SUGAR DERIVATIVES

Compound	Chemical shifts (δ)							Approx J value (Hz)						Solvent
	H1	H2	H3	H4	H5	H6, 6′	OCH_3	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	
22	4·92	5·98	5·98	~4·0	~4·0	4·57	3·42							$CDCl_3$
23	4·89	5·73	5·92	3·38	3·88	4·64	3·42	1·8	~0·5	11·5	0	0	9·5	$CDCl_3$
24	4·98	5·77	5·98	3·57	3·91	4·16	3·42	2·0	~0·5	10·0	−2·0	0	9·5	C_5D_5N
25	4·98	5·92	5·92	4·88	4·20	4·54	3·40	2·0					9·5	C_5D_5N
26	5·06	5·90	6·08	5·40	4·52	4·88	3·40	2·0	~0·5	10·5	0	1·0	9·5	C_5D_5N
27	4·99	6·01	6·01	4·30	3·96	4·05	3·40	1·8			~0	~0	8·5	C_5D_5N
6	4·91	5·90	6·01	4·32	4·18		3·37	1·2	1·0	10·0	~0	1·0	9·2	Acetone-d_6
38	5·12	6·04	6·04	3·97	4·20		3·48					~0	10·5	D_2O

conformation is distorted at C4 and C5 in such a way that all the ring C atoms sit nearly on a plane (sofa conformation) with the ring oxygen out of the plane* (structure **48**, Chart 7). In structure (**48**), H4 becomes less axial and the dihedral angle between H4 and H3 (hence H2) becomes much smaller than 90° so that the magnitude of allylic coupling approaches zero.

It should be noted that recently Ferrier and Sankey[34] reported that in dihydropyran ring systems allylic ester groupings prefer the *quasi*-axial to the *quasi*-equatorial orientation. This rule is now extended to include amides and azides.

An interesting fact is that, in contrast to the olefins discussed above, compound **24** exhibits a considerably large allylic $J_{2,4}$ (Table 3). This may be due to strong intramolecular hydrogen bonding between the 4-amino and the 5-hydroxymethyl groups which would favor a more equatorial orientation for the C4 substituent and render H4 more axial. These data indicate that the unsaturated 4-amino sugar (**24**) assumes the half-chair conformation (**49**) as depicted in Chart 7.†

As for the conformation of the unsaturated amino-uronic acid (**38**), it is to be expected that a large intramolecular interaction would exist between the amino and carboxyl groups which would favor a more equatorial orientation for them. [The IR spectrum of crystalline **38** provides evidence of a zwitterion structure].[12] Unfortunately, compound **38** has adequate solubility only in water and in this solvent the chemical shifts of H2 and H3 are identical which makes resolution of the allylic coupling $J_{2,4}$ impossible. However, the large vicinal coupling $J_{4,5}$ of 10·5 Hz (Table 3) would suggest that the half-chair conformation (**49**) (also called **H1**) for compound **38** is more likely than the sofa.

Other conformational possibilities such as **50** (the alternate "sofa"), **51** (half-chair, **1H**), and **52** (half-boat) are excluded by the large $J_{4,5}$ values which all these unsaturated 4-amino derivatives exhibit. Conformation **53** (half-boat) is also excluded by the following considerations: In this conformation, the dihedral angles defined by H1-H2 and H3-H4 are nearly the same. The coupling constant $J_{3,4}$ should be larger than or equal to $J_{1,2}$ on the basis of the electronegativity effect.[35,36] Experimentally, all compounds listed in Table 3 exhibit $J_{3,4}$ values smaller than $J_{1,2}$ which rules out conformation **53**.

The only remaining conformational possibilities are **54** and **55**, sofa conformations with C-5 out of plane (which we name "C-sofa"). In conformation **54**, H4 and H5 are nearly di-equatorial. The large $J_{4,5}$ values exhibited by the compounds in Table 3 excludes this conformation. In **55**, H4 and H5 are nearly diaxial which would fit the $J_{4,5}$ values of all compounds in Table 3. However, this conformation (**55**) requires a dihedral angle between H4 and H3 (hence H2) of ~90° and should therefore exhibit a large allylic coupling. On this basis conformation **55** can be excluded for all compounds in Table 3 with the exception of compound **24** and possibly **38**. In summary, these NMR studies indicate that, in the solvents employed, the 2,3-unsaturated

* This relationship has been used by Anet[30] to distinguish one sofa conformation for methyl 3,4-dideoxy-6-O-methyl-α-D-*glycero*-hex-3-eno-2-hexopyranosidulose from another sofa conformation.

† It should be noted that in both anomers of methyl 4,6-O-benzylidene-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside, which are rigidly fixed in the half-chair (H1) conformation and in which the dihedral angle between H2 and H4 is approximately 90°, a large allylic coupling $J_{2,4}$ (−2·2 to −2·5 Hz) is exhibited whereas with the *threo* isomers, in which the H2-H4 dihedral angle is around 30°, the $J_{2,4}$ is nearly zero.[15]

derivatives listed in Table 3 exist predominantly in the sofa conformation (**48**) with the exception of compound **24** (and possibly **38**) which takes mainly the half-chair (**49**) or C-sofa (**55**) conformation.

Previous studies[11e,26,34,37] have demonstrated that in unsaturated methyl pyranosides, the anomeric effect[38] stabilizes the axial conformation for this aglycon. This phenomenon is also true for the 2,3-unsaturated 4-amino derivatives described herein, because in the sofa (**48**) or the half-chair-**H1** (**49**) conformations the C-1 methoxyl substituent takes an axial orientation. The fact that most of these compounds (with the exception of **24** and possibly **38**) favor the sofa conformations (**48**) rather than the half-chair (**49**) is probably due to the allylic effect[34] which alters the 4-substituent to a more axial orientation.

EXPERIMENTAL

NMR spectra were recorded on a 60 Mc Varian A-60 spectrometer. M.ps are corrected. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich., and Galbraith Laboratories, Inc., Knoxville, Tenn., U.S.A.

Methyl 4-azido-4-deoxy-2,3-di-O-mesyl-6-O-trityl-α-D-glucoside (**2**). A soln of **1**[5] (10 g) in dry pyridine (25 ml) was cooled to 0° and mesyl chloride (6 ml) was added dropwise over a period of 10 min. The reaction mixture was held at 4° for 16 hr and then diluted with dichloromethane (100 ml). The soln was washed with water (2 × 50 ml), sat $NaHCO_3$ aq (50 ml) and water (50 ml), and the organic layer was dried over $MgSO_4$ and evaporated to a syrup. Traces of pyridine were removed by co-evaporation with toluene, and the syrup was crystallized from hot EtOH to give **2** (12·2 g, 91%), m.p. 165–166°. Recrystallization of this material from EtOH gave analytically-pure product, m.p. 166–167°, $[\alpha]_D^{24}$ +105° (*c* 1·0, Chf). (Found: C, 54·59; H, 5·04; N, 6·61; S, 10·36. $C_{28}H_{31}N_3O_9S_2$ requires: C, 54·45; H, 5·03; N, 6·81, S, 10·35%).

Methyl (methyl 4-azido-4-deoxy-2,6-di-O-mesyl-α-D-glucosid)uronate (**5**). A cooled soln of **4**[5] (291 mg) in dichloromethane (5 ml) and pyridine (1 ml) was treated with mesyl chloride (0·4 ml) for 16 hr. The reaction was diluted with an ice–water mixture and the organic layer was washed successively with water, $NaHCO_3$ aq, water, and dried over Na_2SO_4. The solvent was evaporated and the residue was crystallized from a small amount of EtOH to give 324 mg (68%) of **5**, m.p. 115–116°, $[\alpha]_D^{23}$ +135° (*c* 1·8, Pyr). (Found: C, 29·97; H, 4·33; N, 10·55; S, 15·82. $C_{10}H_{17}N_3O_{10}S_2$ requires: C, 29·77; H, 4·25; N, 10·42; S, 15·90%).

Methyl 2,6-di-O-benzoyl-3,4-O-isopropylidene-β-D-galactopyranoside (**8**). Methyl 3,4-O-isopropylidene-β-D-galactopyranoside[16] (23·4 g, 0·1 mol) was dissolved in pyridine (40 ml) and dichloromethane (100 ml). Benzoyl chloride (35 ml) was added slowly to the stirred, cooled (below 25°) soln. After 3 hr, the reaction was diluted with a mixture of ice–water (250 ml) and dichloromethane (100 ml). The organic layer was washed successively with water, $NaHCO_3$ aq and water, and dried over Na_2SO_4. The soln was evaporated and the residue was dissolved in a small amount of EtOH and re-evaporated. The crystalline residue was recrystallized from EtOH to yield **8**, 42·3 g (95%), m.p. 121–122°, $[\alpha]_D$ +31° (*c* 1·2, Chf). (Found: C, 65·05; H, 5·98. $C_{24}H_{26}O_8$ requires: C, 65·15; H, 5·92%).

The *α-anomer* was prepared analogously but crystallization of this product could not be achieved.

Methyl 2,6-di-O-benzoyl-β-D-galactopyranoside (**9**). Compound **8** (42 g) was dissolved in 88% formic acid (220 ml) at 50°, and the soln was diluted with water (260 ml). A colorless oil separated which crystallized as long needles. After 30 min, crystals were filtered and washed with cold water to give 38·0 g (95%) of **9**, m.p. 155–157°, $[\alpha]^{23}$ +12° (*c* 1·3, Pyr); NMR spectrum in $CDCl_3$: δ 5·28, q, wt 1 assigned to H2 ($J_{1,2}$ = 8·0, $J_{2,3}$ = 9·5 Hz), δ 4·64 (J = 7·2), d, wt 2, assigned to H6, and δ 4·50, d, wt 1 (J = 8·0) assigned to H1. (Found: C, 62·49; H, 5·61. $C_{14}H_{18}O_7$ requires: C, 62·68; H, 5·51%).

The *α-anomer* was prepared from syrupy **8** obtained from 20 g of **7**. After addition of water (250 ml) to the 88% formic acid soln (200 ml), a clear oil separated and was taken up in chloroform (100 ml). The aqueous layer was extracted with further portions (2 × 50 ml) of chloroform and the combined chloroform extracts were washed with $NaHCO_3$ aq (2 × 50 ml) and water (50 ml).

After drying over $MgSO_4$, the soln was evaporated to a yellow syrup, which crystallized slowly on standing. A (1:1) mixture of ether and light petroleum (b.p. 30–60°) was added and the product was filtered and recrystallized (25 g, 59% overall yield from **7**) from EtOH–light petroleum, m.p. 129–130°, $[\alpha]_D^{23}$ +166° (*c* 1·4, Pyr). (Found: C, 62·72; H, 5·53%).

Methyl 2,6-*di*-O-*benzoyl*-3,4-*di*-O-*mesyl*-β-D-*galactoside* (**10**). The dibenzoate **9** (20·1 g) was dissolved in a mixture of dichloromethane (100 ml) and pyridine (100 ml) and cooled to 4°. The soln was treated with mesyl chloride (10 ml) and the reaction mixture remained overnight at room temp. The mixture was diluted with water (100 ml) and the organic layer was washed with water (2 × 100 ml), dried over Na_2SO_4 and evaporated to a syrup which was dissolved in EtOH (100 ml) and re-evaporated. The crystalline residue was dissolved in hot dichloromethane (40 ml) and filtered from insoluble impurities. The filtrate was diluted with EtOH (200 ml) from which compound **10** crystallized, 26 g (93%), m.p. 158–159°, $[\alpha]_D^{23}$ +43° (*c* 1·2, Chf). (Found: C, 49·63; H, 4·66; S, 11·58. $C_{23}H_{26}O_{12}S_2$ requires: C, 49·46; H, 4·69; S, 11·48%).

Methyl 3,4-*di*-O-*mesyl*-β-D-*galactoside* (**13**). To a suspension of **10** (3 g) in MeOH (7 ml), 2M NaOMe in MeOH (3 ml) was added and the mixture was stirred for 20 min. Dowex 50 (H^+) (previously washed with MeOH) was added to the soln until the pH was 6–7. After removal of resin, the soln was evaporated to dryness and the residual syrup was extracted with hot ether. Crystals (0·5 g) were obtained from the ether extract. The remaining syrup was covered with ether and seeded. A total of 1·75 g (93%) of crystalline **13** was obtained, m.p. 150–151°, $[\alpha]_D$ +24° (*c* 1·1, pyr). (Found: C, 30·69; H, 5·15; S, 18·69. $C_9H_{17}O_{10}S_2$ requires: C, 30·95; H, 4·87; S, 18·34%).

Methyl 3,6-*anhydro*-4-O-*mesyl*-β-D-*galactoside* (**15**). Compound **10** (2·0 g) was dissolved in a mixture of MeOH (2 ml) and 2M NaOMe in MeOH soln (2 ml). After 24 hr at room temp, the soln was divided into two equal parts. One part was neutralized with Dowex 50 (H^+, prewashed with MeOH), filtered, evaporated, and the residue extracted with ether to remove methyl benzoate and the residue was benzoylated. Crystalline **10** was obtained indicating that, in spite of the prolonged reaction of **10** with methoxide, debenzoylation was the main reaction. To the other part of the reaction was added MeOH (5 ml) and 2M NaOMe soln (0·75 ml) and the mixture was refluxed. Shortly thereafter, three spots, including starting material, were detected TLC [MeOH-C_6H_6 (1:9)]. Reflux was continued until the spot corresponding to compound **10** disappeared. Concomitantly the fastest-running spot (probably **14**) also disappeared leaving eventually two spots (one of which was due to slow decomposition and stayed at the origin). The reaction was neutralized to pH 6 with conc H_2SO_4 then evaporated to dryness. Water was added to the residue and the mixture was extracted with EtOAc (10 ml × 3). The extracts were dried ($MgSO_4$), evaporated to a syrup which was then covered with ether. Crystallization of compound **15** occurred, 120 mg, m.p. 142–143° (dec), $[\alpha]_D^{23}$ −88° (*c* 0·9, Pyr). (Found: C, 38·06; H, 5·50; S, 12·77. $C_8H_{14}O_7S$ requires: C, 37·80; H, 5·51; S, 12·60%).

Methyl 4,6-O-*benzylidene*-2,3-*di*-O-*mesyl*-β-D-*galactoside*. Methyl, 4,6-O-benzylidene-β-D-galactoside[39] was treated with mesyl chloride in a mixture of pyridine and dichloromethane. A crystalline product was obtained which after recrystallization from EtOH gave m.p. 203–204°, $[\alpha]_D$ 42° (*c* 1·0, Chf). (Found: C, 44·01; H, 4·89; S, 14·53. $C_{16}H_{22}O_{10}S_2$ requires: C, 43·84; H, 5·02; S, 14·63%).

Methyl 2,3-di-O-*mesyl*-β-D-*galactopyranoside*. Treatment of the above benzylidene dimesylate in 80% AcOH for 10 min under reflux followed by evaporation of the solvent left a syrup. Crystallization of the syrup from EtOH gave colorless needles, m.p. 183–183·5°, $[\alpha]_D^{23}$ −7·6° (*c* 1·1, Pyr). (Found: C, 31·02; H, 5·18; S, 18·11. $C_9H_{17}O_{10}S_2$ requires: C, 30·95; H, 4·87; S, 18·34%).

Methyl 4-*azido*-4-*deoxy*-2-O-*mesyl*-6-O-*trityl*-α-D-*glucoside* (**16**). Compound **1**[5] (15 g) was dissolved in 135 ml dry pyridine and cooled at 4°. Mesyl chloride (2·6 ml) was added to the stirred soln. After 16 hr at room temp, the mixture was diluted with dichloromethane (200 ml) and extracted with water (150 ml × 2). The organic layer was dried over Na_2SO_4 and evaporated to a syrup. Traces of pyridine were removed by azeotropic distillation with EtOH. The syrupy residue was crystallized by dissolving it in hot EtOH (100 ml), then the soln was crystallized from a mixture of EtOH (100 ml)–light petroleum (300 ml). After recrystallization from EtOH–light petroleum, compound **16**, 10·5 g (60%) was obtained, m.p. 102–104° (eff). $[\alpha]_D^{23}$ +80° (*c* 1·2 Chf). (Found: C, 60·22; H, 5·39; N, 7·98; S, 5·94. $C_{27}H_{29}O_7N_3S$ requires: C, 60·11; H, 5·41; N, 7·79; S, 5·93%).

Methyl 2,3-*anhydro*-4-*azido*-6-O-*benzoyl*-4-*deoxy*-α-D-*mannoside* (**19**). Compound **16** (10 g) was dissolved in dichloromethane (20 ml) and treated with 2M NaOMe in MeOH (10 ml) and refluxed for 2 hr. The mixture was evaporated to dryness, the residue was extracted with dichloromethane (100 ml) and the extract was washed with water (100 ml × 2), dried over Na_2SO_4, and evaporated to syrupy **17**. The syrup was dissolved in warm (40–45°) AcOH (80 ml) and the soln was diluted with water (20 ml). The mixture was heated on a steam-bath for 20 min and cooled to room temp. After 4 hr, precipitated triphenyl carbinol (3.7 g) was filtered and the filtrate was evaporated to dryness. Traces of AcOH were removed by azeotropic distillation with toluene. The residual syrup, consisting mainly of **18** contaminated with triphenyl carbinol, was dissolved in a mixture of dichloromethane (50 ml) and pyridine (30 ml). The mixture was treated with benzoyl chloride (10 ml). After 12 hr, the mixture was diluted with ice–water (100 ml), and the organic layer

was washed with water, $NaHCO_3$ aq, water and dried over Na_2SO_4. The soln was evaporated to dryness. Traces of pyridine were removed by azeotropic distillation with EtOH and then with benzene. The syrup was chromatographed[40] over Silica Gel G (250 g) using 5% EtOAc in benzene (v/v). Compound **19** (5·3 g, 94%) was obtained from the column n_D^{23} 1·5343, $[\alpha]_D^{33}$ +111° (*c* 1·0, Chf). (Found: C, 55·04; H, 4·95; N, 13·97. $C_{14}H_{15}O_5N_3$ requires: C, 55·08; H, 4·95; N, 13·76%).

Methyl 4-*azido*-6-O-*benzoyl*-3,4-*dideoxy*-3-*iodo*-α-D-*altroside* (**20**). A mixture of compound **19** (3·5 g), NaI (7·0 g), NaOAc (0·4 g), and AcOH (7·2 ml) in acetone (50 ml) was refluxed for 8 hr. The acetone was removed by evaporation and the residue was partitioned between dichloromethane (100 ml) and water (100 ml). The organic layer was washed with water, 0·1 M $Na_2S_2O_3$, water and dried over Na_2SO_4. After evaporation to dryness a crystalline residue was obtained which was recrystallized from EtOH. Compound **20** was obtained as slightly yellow needles, 4·2 g (84%), m.p. 121–122°, $[\alpha]_D^{24}$ +108° (*c* 0·9, Chf). (Found: C, 39·01; H, 3·70; N, 9·75; I, 29·33. $C_{14}H_{16}O_5IN_3$ requires: C, 38·82; H, 3·72; N, 9·72; I, 29·29%).

Methyl 4-*azido*-6-O-*benzoyl*-2,3,4-*trideoxy*-α-D-*erythro*-*hex*-2-*enopyranoside* (**22**). Compound **20** (615 mg) and mesyl chloride (0·14 ml) were dissolved in pyridine (10 ml) and refluxed for 5 min. The reaction was poured into an ice–water mixture (70 ml) and extracted with ether (40 ml × 3). The combined extracts were washed successively with water, 0·1M $Na_2S_2O_3$ and water. After drying over Na_2SO_4, the ether was evaporated. Traces of pyridine were removed by azeotropic distillation with ethanol. The residue **22** (387 mg, 94%) was analytically pure, n_D^{23} 1·5349, $[\alpha]_D^{24}$ +116° (*c* 1·0, Chf). (Found: C, 58·41; H, 5·09; N, 14·39. $C_{14}H_{15}O_4N_3$ requires: C, 58·13; H, 5·23; N, 14·53%).

Methyl 4-*amino*-6-O-*benzoyl*-2,3,4-*trideoxy*-β-D-*erythro*-*hex*-2-*enopyranoside* (**23**). To a MeOH soln (25 ml) of **22** (500 mg) was added M NaOAc and sodium dithionite (1 g) and the mixture was refluxed for 30 min. During this reaction period, 1 g sodium dithionite was added at every 5 min. The MeOH was removed under reduced press and the residue was extracted with ether (10 ml × 2) to remove unreacted starting material and the N-benzoyl derivative (see synthesis of compound **26**) which had formed during reduction. The aqueous layer was adjusted to pH ~ 8 by slow addition of solid $NaHCO_3$, and extracted with EtOAc (15 ml × 4). Examination of the EtOAc solution by TLC (10% MeOH in Chf) showed that it contained only one product. After drying over Na_2SO_4, the solvent was evaporated to a syrup, 208 mg (45·7%). This product **23** was sufficiently pure for the next step.

Methyl 4-*amino*-2,3,4-*trideoxy*-α-D-erythro-*hex*-2-*enopyranoside* (**24**). The amino compound (**23**, 160 mg) was dissolved in MeOH (1 ml) and M NaOMe in MeOH soln (0·2 ml) was added. After 16 hr at room temp, starting material was absent and two products were detected by TLC. The faster moving component was identical with that of the N-benzoyl isomer of **23** produced by benzoyl migration. The solvent was evaporated and the residue was chromatographed on a Silica Gel G column (10 × 2·2 cm, 20 g) using 1:4 MeOH–Chf mixture (v/v) as solvent. The N-benzoate eluted from the column first was contaminated with a small amount of compound **24**. Pure **24** was eluted from the column as the second fraction. Upon evaporation of the second fraction, compound **24** was obtained, 84 mg (87%), n_D^{24} 1·4968, $[\alpha]_D^{23}$ +130 (*c* 1·2, EtOH). (Found: C, 50·16; H, 8·26; N, 8·15. $C_7H_{13}O_3N$. 1/2 H_2O requires: C, 50·00; H, 8·33; N, 8·33%. The NMR spectrum showed this sample to contain a half molecule of water).

The first fraction was evaporated and the residue (20 mg) was benzoylated with benzoyl chloride (0·03 ml) in pyridine (1 ml) for 3 hr. The solvent was evaporated off, the residue was dissolved in dichloromethane and extracted successively with water, $NaHCO_3$ aq and water. After drying over sodium sulfate, the solvent was evaporated and the residue was seeded with authentic **26** (see below) and recrystallized from EtOH; colorless needles, m.p. 154–155° undepressed on admixture with an authentic sample obtained (see below) by benzoylation of **23**.

Methyl 4-*acetamido*-6-O-*acetyl*-2,3,4-*trideoxy*-α-D-erythro-*hex*-2-*enopyranoside* (**25**). Compound **24** (42 mg) was acetylated in a mixture of pyridine (1 ml) and Ac_2O (0·5 ml) for 6 hr. After evaporation of the solvent followed by azeotropic distillation with EtOH, the residue was chromatographed on a Silica Gel G column (5 cm × 2·2 cm, 10 g) using 10% EtOAc in benzene as solvent. The appropriate fractions were combined and evaporated to give **25** as a syrup, 50 mg, n_D^{23} 1·5349 $[\alpha]_D^{24}$ +226° (*c* 1·2, Chf). (Found: C, 54·08; H, 7·26; N, 5·55. $C_{11}H_{17}O_5N$ requires: C, 54·31; H, 7·05; N, 5·76%).

Methyl 4-*benzamido*-6-O-*benzoyl*-2,3,4-*trideoxy*-α-D-erythro-*hex*-2-*enopyranoside* (**26**). Compound **23** (39 mg) was benzoylated with benzoyl chloride (0·75 ml) in pyridine (1·5 ml) for 17 hr at room temp. Dichloromethane (7 ml) was added to the reaction and the mixture was washed with ice–water. After drying the organic layer over Na_2SO_4, the solvent was evaporated and the residue was chromatographed on a Silica Gel G column (2·2 × 5 cm, 10 g) using 10% EtOAc in benzene as solvent. Colorless needles (42 mg) were obtained after evaporation of solvent. Recrystallization from EtOH gave an analytical sample, m.p.

155–156°, $[\alpha]_D^{23}$ +151° (*c* 1·1, Chf). (Found: C, 68·42; H, 5·69; N, 3·71. $C_{21}H_{21}O_5N$ requires: C, 68·64; H, 5·77; N, 3·81%).

Methyl 4-*azido*-2,3,4-*trideoxy*-α-D-erythro-*hex*-2-*enopyranoside* (27). Compound **22** (122 mg) was dissolved in MeOH and treated with 1M methanolic NaOMe (1 ml) overnight at room temp. After evaporation, the residue was chromatographed over a column of Silica Gel G (10 g, 2·2 cm × 5 cm) with 10% MeOH in Chf. Pure **27** was obtained as a colorless syrup, 63 mg, n_D^{23} 1·4987, $[\alpha]_D^{23}$ +287° (*c* 0·9, EtOH). (Found: C, 45·71; H, 6·05; N, 23·00. $C_7H_{11}O_3N_3$ requires: C, 45·40; H, 5·99; N, 22·69%).

Methyl 4-*azido*-3-O-*benzoyl*-4-*deoxy*-2-O-*mesyl*-6-O-*trityl*-α-D-*glucoside* (**29**). Benzoyl chloride (6 ml) was added to a cooled soln of compound **16** (11·5 g) in dichloromethane (60 ml) and pyridine (12 ml) and the reaction was left standing overnight at room temp. Water (60 ml) was added and the organic layer was washed with water, $NaHCO_3$ aq and water. After drying over Na_2SO_4, the solvent was evaporated. A small amount of pyridine was removed by azeotropic distillation with EtOH. The residue was crystallized from EtOH to give colorless needles, 1·2 g (88%), m.p. 175–177°, $[\alpha]_D^{23}$ +78° (*c* 1·7, Chf). (Found: C, 63·57; H, 5·19; N, 6·43; S, 5·09. $C_{34}H_{33}O_8N_3S$ requires: C, 63·44; H, 5·17; N, 6·53; S, 4·98%).

Methyl 4-*azido*-3-O-*benzoyl*-4-*deoxy*-2-O-*mesyl*-α-D-*glucoside* (**30**) *and its* 6-O-*benzoate*. Compound **29** (10 g) was suspended in 88% formic acid (50 ml) and stirred at 45° until a clear soln was obtained. The mixture was cooled to room temp and the precipitated triphenyl carbinol (3·7 g) was filtered and washed with a small amount of 88% formic acid. The filtrate and washings were combined and diluted with water (350 ml) and extracted with dichloromethane (100 ml). The dichloromethane was washed with water (100 ml × 2), $NaHCO_3$ aq (75 ml × 2) and water. After drying over Na_2SO_4, the soln was evaporated. The syrupy **30** obtained was still contaminated with triphenyl carbinol.

Crude **30** (1 g) was benzoylated with benzoyl chloride and pyridine and the reaction mixture was fractionated by Silica Gel G column chromatography. The crystalline 6-O-benzoyl derivative of **30** (0·82 g) was recrystallized from EtOH–light petroleum, m.p. 149–151°, $[\alpha]_D^{26}$ +175° (*c* 1·0, Chf). (Found: C, 52·10; H, 4·55; N, 8·28; S, 6·33. $C_{22}H_{33}O_9N_3S$ requires: C, 52·27; H, 4·59; N, 8·31; S, 6·34%).

Methyl (*methyl* 4-*azido*-3-O-*benzoyl*-4-*deoxy*-2-O-*mesyl*-α-D-*glucosid*)*uronate* (**32**). Crude **30** (5 g) was dissolved in a 1:1 AcOH–acetone mixture (50 ml) and finely pulverized $KMnO_4$ (1·5 g) was added. The mixture was stirred at room temp and after 1 hr additional oxidant (1·0 g) was added, followed by another charge (1·0 g) after 1·5 hr. After stirring an additional hr, water (10 ml) followed by $NaHSO_3$ (20 g) was added to the vigorously-stirred mixture until the brown color of MnO_2 disappeared. The mixture was filtered and the filtrate was concentrated. The residue was extracted with dichloromethane (50 ml), and after drying over Na_2SO_4, the soln was evaporated to a syrup which was dissolved in MeOH (50 ml) and treated with excess diazomethane at 5°. TLC [EtOAc–C_6H_6 (1:9)] showed that the mixture contained only two components, triphenyl carbinol and the desired compound **32**. Excess diazomethane was decomposed by addition of AcOH, and the soln was concentrated. The residue was dissolved in a small amount of 10% EtOAc in benzene and chromatographed on a column of Silica Gel G (200 g). Compound **32** (1·15 g) was isolated as a syrup, $[\alpha]_D^{24}$ +144° (*c* 1·5, Chf). (Found: C, 44·72; H, 4·55; N, 9·67; S, 7·47. $C_{16}H_{19}O_9N_3S$ requires: C, 44·75; H, 4·46; N, 9·79; S, 7·47%).

Methyl (*methyl* 2,3-*anhydro*-4-*azido*-4-*deoxy*-α-D-*mannosid*)*uronate* (**33**). Crude **18** (2·0 g) was dissolved in a 1:1 mixture of AcOH and acetone (40 ml) and powdered $KMnO_4$ (2 g) was added. The mixture was stirred overnight at room temp. An additional charge of $KMnO_4$ (2 g) was added and the mixture was stirred for 4 more hr, then diluted with 5 ml water. $NaHSO_3$ was added to the vigorously-stirred suspension until the brown color disappeared. After filtration, the inorganic solids were washed with acetone–AcOH mixture (1:1). The combined filtrate and washings were evaporated to a small volume and diluted with water (40 ml) and extracted with ether (40 ml × 3). The aqueous layer was adjusted to pH ~3 with conc HCl and extracted with EtOAc (40 ml × 3). After drying over Na_2SO_4, the soln was evaporated to a syrup (**34**, 480 mg). The syrup (**34**, 400 mg) was dissolved in MeOH and treated with diazomethane. After decomposing the excess diazomethane with AcOH, the solvent was removed and the residue was chromatographed over a column of Silica Gel G (10 g) using 10% EtOAc in benzene. Compound **33** (260 mg) was obtained as a colorless syrup, n_D^{23} 1·4799, $[\alpha]_D^{23}$ +68° (*c* 1·5, Chf). (Found: C, 41·63; H, 4·94; N, 18·01 $C_8H_{11}O_5N_3$ requires: C, 41·89; H, 4·81; N, 18·31%).

Methyl (*methyl* 4-*azido*-2,3,4-*trideoxy*-α-D-erythro-*hex*-2-*enopyranosid*)*uronate* (**6**). A mixture of compound **33** (230 mg), NaI (710 mg), NaOAc (42 mg) and AcOH (0·1 ml) in acetone (5 ml) was refluxed for 40 hr. After concentration of the mixture *in vacuo*, the residue was partitioned between water (20 ml) and dichloromethane (20 ml). The organic layer was washed with water, 0·1M $Na_2S_2O_3$ and water. After

drying over Na_2SO_4, the soln was concentrated to dryness. The iodohydrin **35** (273 mg) was obtained as reddish brown crystals.

The crude iodohydrin (203 mg) was dissolved in pyridine (5 ml) and mesyl chloride (0·06 ml) was added. The mixture was left overnight at room temp, after which it was diluted with water (20 ml) and dichloromethane (20 ml). The organic layer was washed with water, 0·1M $Na_2S_2O_3$ and water. After drying over Na_2SO_4, the soln was concentrated and the residue was chromatographed on a Silica Gel G column (5 cm × 2·2 cm, 10 g) with 20% EtOAc in benzene. Pure compound **6** was obtained as a colorless syrup, 107 mg, $[\alpha]_D^{23}$ +201 (*c* 1·8, MeOH). (Found: C, 45·09; H, 5·36; N, 19·41. $C_8H_{11}O_4N_3$ requires: C, 45·07; H, 5·20; N, 19·71%).

*Methyl 4-amino-2,3,4-trideoxy-α-*D*-*erythro*-hex-2-enopyranosiduronic acid* (**38**). To a soln of **6** (500 mg) in MeOH (18 ml) was added 0·67M phosphate buffer (pH 7, 15 ml) and solid sodium dithionite (2·4 g). The mixture was heated under reflux with vigorous stirring for 20 min, after which it was cooled and the MeOH removed by evaporation *in vacuo*. Water (10 ml) and benzene (10 ml) were added. The aqueous layer was separated and extracted with benzene (10 ml). The combined benzene solns were dried over $MgSO_4$ and concentrated to a syrup (unreacted **6**, 140 mg). The aqueous layer was neutralized with solid $NaHCO_3$ (2 g) and extracted with Chf (10 ml × 5). The combined extracts [one spot on TLC, MeOH–Chf (1:9)] were dried over $MgSO_4$ and concentrated to a syrup, compound **37** (170 mg).

This syrup was dissolved in MeOH (5 ml) and diluted with water (5 ml). N NaOH was added dropwise until hydrolysis of the ester was complete as indicated by TLC. The mixture was neutralized with Amberite IRC-50 (H^+, 5 ml). The resin was filtered and after concentration of the filtrate, crude compound **38** (162 mg) was obtained. A sample was dissolved in water and after treatment with charcoal, the filtrate was concentrated to a small volume. The pH of the soln was adjusted to 4 with AcOH. Acetone was then added, whereupon crystallization occurred slowly. Slightly yellow crystals were obtained, m.p. >270° (dec), $[\alpha]_D^{23}$ +30·5 (*c* 0·29, H_2O). The IR spectrum of **38** was reported previously.[12] Compound **38** was slightly hygroscopic. (Found: C, 47·36; H, 6·54; N, 7·21. $C_7H_{11}O_4N{\cdot}\frac{1}{2}H_2O$ requires: C, 47·32; H, 6·52; N, 7·88%).

*Methyl (methyl 4-acetamido-2,3,4-trideoxy-α-*D*-*erythro*-hexopyranosid)uronate* (**39**)

Method (A) from compound **6**. Compound **6** (150 mg) was dissolved in MeOH (10ml) and hydrogenated over Adams catalyst (75 mg) for 90 min. After consumption of about one mole of H_2 the catalyst was removed by filtration and the filtrate was treated with Ac_2O (0·3 ml). After 10 min at room temp, the reaction mixture was concentrated. Traces of AcOH were removed by azeotropic distillation with toluene. The crystalline residue was recrystallized from Chf–light petroleum (30–60°) to give compound **39** (160 mg). A second recrystallization afforded an analytical sample, m.p. 145–146°, $[\alpha]_D^{23}$ +87° (*c* 1·0 Chf). (Found: C, 52·35; H, 7·68; N, 5·90. $C_{10}H_{17}O_5N$ requires: C, 52·00; H, 7·36; N, 6·06%).

Method (B) from compound **38**. A mixture of compound **38** (57 mg) and Adams catalyst (30 mg) in MeOH (6 ml) was shaken in a H_2 atm for 90 min. After removal of the catalyst, the filtrate was concentrated and the residue was dissolved in water (2 ml) and N NaOH (0·4 ml). Ac_2O (0·1 ml) was then added to the soln and the mixture was stirred vigorously for 5 min. The pH of the mixture was then adjusted to pH ~7 with N NaOH, and more Ac_2O (0·1 ml) was added. After 5 min the soln was cooled to 0° and Dowex 50 (H^+ form, 5 ml) was added and the mixture was stirred for 2 min. After removal of the resin, concentration of the filtrate afforded a crystalline residue which was dissolved in MeOH (6 ml), cooled to 0°, and treated dropwise with ethereal diazomethane. When the reaction was ~90% completed (as indicated by TLC), the mixture was concentrated to a semi-crystalline residue. The major component of this residue was isolated by chromatography on a column of Silica Gel G (2·2 cm × 5 cm, 10 g) in 5% EtOH in benzene. After concentration of the appropriate fractions, crystalline product (45 mg) was obtained. Recrystallization from Chf–light petroleum gave a sample identical with **39**.

*Methyl 2,3-anhydro-4-azido-4-deoxy-6-O-trityl-α-*D*-alloside* (**41**). A soln of **2** (11·1 g) in dichloromethane (80 ml) was cooled to 4° and treated with 2M NaOMe in MeOH (40 ml). After standing at 4° for 16 hr, the mixture was kept at room temp for 24 hr. Dichloromethane (70 ml) and water (80 ml) were then added and the aqueous layer was extracted with dichloromethane (50 ml). The combined organic solns were washed several times with water until the aqueous washings were neutral. The organic layer was dried over $MgSO_4$, and evaporated to a thick syrup which was crystallized from MeOH, 6·0 g (69%), m.p. 98–100°. Recrystallization from MeOH gave an analytical sample, m.p. 99·5–101°, $[\alpha]_D^{24}$ +122° (*c* 1·0, Chf). (Found: C, 70·22; H, 5·85; N, 9·75. $C_{26}H_{25}O_4N_3$ requires: C, 70·50; H, 5·65; N, 9·84%).

*Methyl 2,3-anhydro-4-azido-4-deoxy-α-*D*-allopyranoside* (**12**). Water (2·5 ml) was added to a solution of **41** (1·0 g) in AcOH (10 ml) and the soln was heated at 100° for 10 min, and then cooled to 4°. Precipitated

triphenylcarbinol was removed by filtration and the filtrate was evaporated to dryness. Traces of AcOH were removed by azeotropic distillation with toluene. The residue was crystallized from benzene–light petroleum, 0·4 g, (93%), m.p. 66–67°. Recrystallization from the same solvent system gave an analytical sample, m.p. 67–68°, $[\alpha]_D^{24}$ +236° (*c* 1·0, Chf). (Found: C, 44·69; H, 5·77; N, 19·02. $C_7H_{11}O_4N_3 \cdot \frac{1}{8}C_6H_6$ requires: C, 44·86; H, 5·64; N, 19·61%).

Methyl 2,3-*anhydro*-4-*azido*-6-O-*benzoyl*-4-*deoxy*-α-D-*alloside* (**42**). Benzoylation of **12** (2 g) in dichloromethane (8 ml) and pyridine (2 ml) with benzoyl chloride (2 ml) gave crystalline **42** in quantitative yield. Recrystallization from EtOH gave an analytical sample, m.p. 89–91°, $[\alpha]_D^{23}$ +213° (*c* 0·7, Chf). (Found: C, 54·86; H, 5·03; N, 13·59. $C_{14}H_{15}O_5N_3$ requires: C, 55·08; H, 4·95; N, 13·76%).

Compound **22** *from* **42**. A mixture of **42** (1·44 g), NaI (2·90 g), NaOAc (0·15 g), AcOH (3 ml) in acetone (20 ml) was refluxed for 4 hr and evaporated to dryness. The residue was partitioned between dichloromethane (40 ml) and water (40 ml). The organic layer was washed with water, 0·1M $Na_2S_2O_3$, and water. After drying over Na_2SO_4, the soln was evaporated to a semi-crystalline residue (**43**, 2·0 g) which, as indicated by NMR examination, consisted of the 2-iodo-*altro* (~90%) and the 3-iodo-*gluco* (~10%) derivatives. The mixture **43** (1·46 g) was dissolved in pyridine (15 ml) and refluxed for 20 min with mesyl chloride (0·5 ml). The reaction mixture was concentrated to about 7 ml and partitioned between ether (40 ml) and water (40 ml). The ether was washed with water, 0·1M $Na_2S_2O_3$, and water. After drying over Na_2SO_4, the soln was evaporated to a syrup and the residue was chromatographed over Silica Gel G column (10 cm × 2·2 cm, 20 g) using 5% EtOAc in benzene. Compound **22** (762 mg) thus obtained was identical with respect to its IR and NMR spectra with a sample obtained previously from **20**.

Methyl 2,3-*anhydro*-4-*azido*-4-*deoxy*-α-D-*allosiduronic acid* (**44**). Compound **12** (2·8 g) was dissolved in AcOH (20 ml), acetone (10 ml), and water (10 ml). Powdered $KMnO_4$ (5 g) was added to the cooled, stirred mixture. After 2·5 hr at room temp, water (20 ml) was added and the suspension was stirred vigorously during the addition of $NaHSO_3$. When the MnO_2 was dissolved, the mixture was evaporated to dryness under reduced press (below 35°) and the residue was dissolved in water (20 ml). Extraction of the soln with dichloromethane (20 ml × 2) removed unreacted starting material. Acidification of the aqueous soln with conc HCl to pH ~3 was followed by extraction with EtOH (10 ml × 10). The combined organic extracts were washed with 0·01N HCl (10 ml) and water (10 ml) and dried over $MgSO_4$. Evaporation of the soln to dryness gave a syrup which crystallized readily to give **44** (1·60 g, m.p. 129–131°). One recrystallization from benzene afforded an analytical sample, m.p. 136–138°, $[\alpha]_D^{24}$ +230° (*c* 1·39 Chf). (Found: C, 39·35; H, 4·33; N, 18·96. $C_7H_9O_5N_3$ requires: C, 39·10; H, 4·18; N, 19·55%).

Methyl (*methyl* 2,3-*anhydro*-4-*azido*-4-*deoxy*-α-D-*allosid*)*uronate* (**45**). Compound **44** (1·50 g) was dissolved in MeOH (10 ml) and the soln was cooled to 0°. A soln of diazomethane in ether was added in slight excess. After standing at 0° for 10 min, the excess diazomethane was decomposed with AcOH and the soln was evaporated to dryness. The crystalline residue of **45** (1·56 g, 98%, m.p. 65–66°) was recrystallized from benzene–heptane, m.p. 66–67°, $[\alpha]_D^{24}$ +232° (*c* 1·3, Chf). (Found: C, 41·93; H, 4·95; N, 17·85. $C_8H_{11}N_3O_5$ requires: C, 41·89; H, 4·81; N, 18·31%).

Preparation of **6** *from* **45**. Compound **45** (1·50 g) was added to dry acetone (25 ml) containing NaI (4·5 g), NaOAc (0·24 g) and AcOH (7·2 ml). The mixture was refluxed for 20 min after which TLC showed that all the starting material was consumed and two new spots were detected. The soln was evaporated to dryness and water (25 ml) and Chf (30 ml) were added. The two layers were separated and the aqueous layer was washed with 25 ml Chf. The combined organic layers were washed with 0·1M $Na_2S_2O_3$ (25 ml) and water (10 ml). After drying over $MgSO_4$ the Chf soln was evaporated to dryness. Traces of AcOH were removed by azeotropic distillation with toluene. The residue **46** consisted of the 2-iodo *altro* and the 3-iodo *gluco* derivatives in a 2:1 ratio as determined by NMR spectroscopy.

This mixture of compounds **46** was dissolved in pyridine (10 ml) and treated with 0·8 ml mesyl chloride. After heating the solution at 100° for 5 min it was diluted with water (30 ml) and Chf (50 ml). The aqueous layer was extracted with Chf (50 ml). The combined Chf solns were washed with 0·1M $Na_2S_2O_3$ (40 ml) and water. After drying over $MgSO_4$, the soln was evaporated to a syrup from which pyridine was removed by azeotropic distillation with toluene. The mixture was separated by column chromatography on Silica Gel G (100 g) in a solvent which contained 2% MeOH in a 2:1 (v/v) mixture of light petroleum (30–60°) and benzene. Compound **6** was eluted first and, after evaporation of the solvent, was isolated as a mobile liquid (0·87 g, 63%). The IR and NMR spectra of **6** thus obtained were identical with those exhibited by **6** obtained previously from compound **33**.

Methyl (*methyl* 4-*azido*-3,4-*dideoxy*-3-*iodo*-2-O-*mesyl*-α-D-*glucosid*)*uronate* (**47**). The second component eluted from the above column was compound **47** which was obtained in crystalline form (0·58 g, 28%) by

evaporation of solvent. Recrystallization from Chf–light petroleum gave an analytical sample, m.p. 95–97°, $[\alpha]_D^{23}$ +89° (*c* 1·0, Chf). Found: C, 24·87; H, 3·15; N, 9·63, S, 7·25; I, 29·83. $C_9H_{14}O_7N_3SI$ requires: C, 24·80; H, 3·21; N, 9·53; S, 7·33; I, 29·40%).

Compound **6** *from* **47**. A mixture of **47** (442 mg), Zn dust (212 mg) and tetramethylammonium chloride (23 mg) in pyridine (3 ml) was refluxed for 20 min under N_2. Insoluble inorganic material was removed by filtration and washed with a small amount of pyridine. The combined pyridine solns were evaporated to dryness. The residue was suspended in water (10 ml) and extracted with ether (10 ml × 4). The ether extracts were washed with water, 0·1M $Na_2S_2O_3$, and water. After drying over Na_2SO_4, the ether soln was evaporated and the residue was chromatographed over a Silica Gel G column (10 g, 2·2 cm × 5 cm) using 5% EtOAc in benzene. Compound **6** (186 mg) was obtained as a colorless liquid which was identical with that previously obtained from **33**.

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