Semisynthetic Aminoglycoside Antibacterials. Part 8.[1,2] Synthesis of Novel Pentopyranosyl and Pentofuranosyl Derivatives of Gentamine C_1 and C_{1a}

By **D. Huw Davies, Max Kugelman, Paul Lee, Charles E. Luce, Alan K. Mallams,* James B. Morton, Surinderjit S. Saluja,** and **John J. Wright,** Research Division, Schering–Plough Corporation, Bloomfield, New Jersey 07003, U.S.A.
George Detre, Masato Tanabe, and **Dennis M. Yasuda,** Life Sciences Division, Stanford Research Institute, Menlo Park, California 94025, U.S.A.

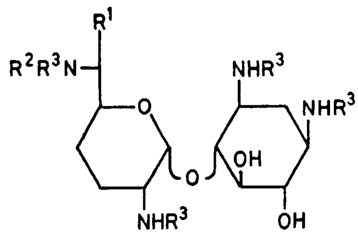
The syntheses of a variety of 6-*O*- and 5-*O*-pentopyranosyl and -pentofuranosyl derivatives from 1,3,2′,6′-tetrakis-*N*-benzyloxycarbonylgentamine C_{1a} and C_1 are described. These include neutral glycosides as well as 3-amino-3-deoxy- and 3-deoxy-3-methylamino-glycosides. The solution conformations of these novel semisynthetic aminoglycoside antibacterials are described.

GAROSAMINE,[3] a novel branched chain 3-deoxy-3-methylaminopentopyranoside, occurs widely as the 6-*O*-glucosyl unit in most of the gentamicin–sisomicin family of aminoglycoside antibiotics[4] produced by various species of *Micromonospora*. Several minor components isolated from these fermentations have been shown to contain other novel 6-*O*-pentopyranosyl units. Thus gentamicin A,[5] and 66-40B[6] have been shown to contain gentosamine (3-deoxy-3-methylamino-α-D-xylopyranoside),[5,7] while gentamicin A_4[8] contains the 3″-*N*-formyl derivative of gentosamine. Another novel pentopyranoside, 3-deoxy-3-methylamino-β-L-arabinopyranoside,[7] occurs in 66-40D,[6] gentamicin A_1,[8] and gentamicin A_3,[8] while the de-*N*-methyl derivative of garosamine has recently been shown to occur in 66-40G.[9] A neutral 6-*O*-pentopyranoside, α-D-xylopyranoside, has also been found to occur in gentamicin A_2.[10] At the time this work was performed, none of these pentopyranosides, with the exception of garosamine, had been found to occur on a gentamine unit. It was therefore of interest to us to prepare these and other pentopyranosyl and pentofuranosyl derivatives from gentamine C_1 (1) and C_{1a} (2).[11] Recently, Berdy[12] has isolated the 6-*O*-3-deoxy-3-methylamino-β-L-arabinopyranosyl derivatives of gentamine C_1 (5), C_2 (6), and C_{1a} (7) as minor components of the gentamicin fermentation.

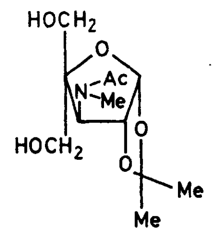
Our synthesis of (7) was accomplished as follows. 3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*N*-methylacetamido-α-D-galactofuranose (13)[13] was hydrolysed with aqueous acetic acid to remove the 5,6-isopropylidene group selectivity. The resulting glycol was cleaved with sodium metaperiodate and reduction of the intermediate aldehyde afforded, after *N*-acetylation and chromatography, a 57% yield of 3-deoxy-1,2-*O*-isopropylidene-3-*N*-methylacetamido-β-L-arabinofuranose (14) along with some unchanged starting material (13). Two by-products were also isolated, namely 3-deoxy-4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3-*N*-methylacetamido-β-L-*threo*-pentofuranose (15) and the dimer (16). This observation led one of us to develop an elegant synthesis of garosamine and related sugars.[13]

Hydrolysis of the isopropylidene derivative (14) with Amberlite IR 120 (H^+) resin gave 3-deoxy-3-*N*-methylacetamido-α- and -β-L-arabinopyranose (17) and (18) respectively. Methanolysis, followed by re-*N*-acetylation afforded the methyl glycosides (19) and (20), which on treatment with sodium hydride and benzyl bromide gave methyl 2,4-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-L-arabinopyranoside (21) and (22) respectively. The latter on acidic hydrolysis with a mixture of sulphuric and acetic acids, followed by acetylation with acetic anhydride and sodium acetate, gave 1-*O*-acetyl-2,4-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-L-arabinopyranose (23) and (24). Treatment of the latter with acetyl chloride in the presence of dry hydrogen chloride afforded 2,4-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-β-L-arabinopyranosyl chloride (25). Condensation of the latter with 1,3,2′,6′-tetrakis-*N*-benzyloxycarbonylgentamine C_{1a} (4), in the presence of silver toluene-*p*-sulphonate in dichloromethane, afforded *O*-2,4-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-β-L-arabinopyranosyl-(1 → 6)-1,3,2′,6′-tetrakis-*N*-benzyloxycarbonylgentamine C_{1a} (8). Reduction with sodium in liquid ammonia followed by basic hydrolysis gave *O*-3-deoxy-3-methylamino-β-L-arabinopyranosyl-(1 → 6)-gentamine C_{1a} (7).[12] The rotation of (7) was in agreement with the proposed β-L-linkage and the ^1H n.m.r. spectrum revealed a doublet ($J_{1eq'',2ax''}$ 4 Hz) at δ_H 5.09 which was also consistent with such a linkage. The mass spectral data are given in Table 1.[14] The ^{13}C n.m.r. parameters for (7) (Table 2) were in agreement with those expected for a (1 → 6)-linked β-L-arabinopyranoside.[6]

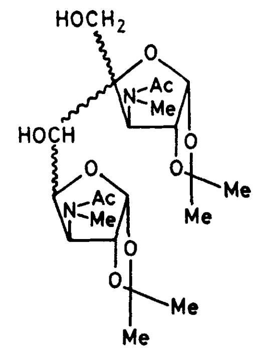
The synthesis of a series of D-xylo-analogues was undertaken next. Methyl 3-acetamido-3-deoxy-β-D-xylopyranoside (26)[7] was converted into the 2,4-di-*O*-benzyl derivative (27) and the latter on acetolysis as described above gave 3-acetamido-1-*O*-acetyl-2,4-di-*O*-benzyl-3-deoxy-α- and -β-D-xylopyranose (28) and (29). Further reaction with acetyl chloride and dry hydrogen chloride afforded 3-acetamido-2,4-di-*O*-benzyl-3-deoxy-α-D-xylopyranosyl chloride (30). The chloro-sugar (30) was condensed with 1,3,2′,6′-tetrakis-*N*-benzyloxycarbonylgentamine C_{1a} (4) to give a mixture of three protected pseudotrisaccharides, namely (9), (39), and (43). The mixture was reduced with sodium in liquid ammonia and then subjected to basic hydrolysis to give three products. The first of these, *O*-3-amino-3-deoxy-β-D-xylopyranosyl-(1 ⟶ 6)-gentamine C_{1a} (40), showed a low positive specific rotation, consistent with a β-D-glycoside. The signal due to 1″-H, however, was obscured by the D_2O peak at *ca.* δ_H 4.67 so that no coupling constant for $J_{1ax'',2ax''}$ could be determined. The ^{13}C n.m.r. spectrum of (40) (Table 2) exhibited a signal at δ_C 105.3 for C-1″ clearly supporting the β-linkage. The remaining carbons of the xylopyranosyl ring gave signals that confirmed this assignment. It was also evident from Table 2 that (40) was (1 ⟶ 6) linked. The second product isolated was *O*-3-amino-3-deoxy-α-D-xylopyranosyl-(1 ⟶ 6)-gentamine C_{1a} (10) and the rotation was in



(1) $R^1 = R^2 = Me, R^3 = H$
(2) $R^1 = R^2 = R^3 = H$
(3) $R^1 = R^2 = Me, R^3 = Z$
(4) $R^1 = R^2 = H, R^3 = Z$
$Z = PhCH_2O{\cdot}CO$



(15)



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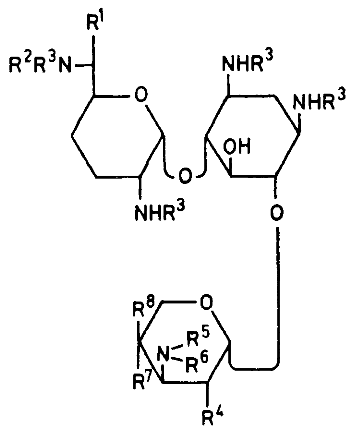
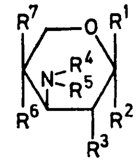
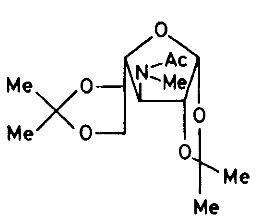


(5) $R^1 = R^2 = R^6 = Me, R^3 = R^5 = R^7 = H, R^4 = R^8 = OH$
(6) $R^1 = R^6 = Me, R^2 = R^3 = R^5 = R^7 = H, R^4 = R^8 = OH$
(7) $R^1 = R^2 = R^3 = R^5 = R^7 = H, R^4 = R^8 = OH, R^6 = Me$
(8) $R^1 = R^2 = R^7 = H, R^3 = Z, R^4 = R^8 = OCH_2Ph, R^5 = Ac, R^6 = Me$
(9) $R^1 = R^2 = R^6 = R^8 = H, R^3 = Z, R^4 = R^7 = OCH_2Ph, R^5 = Ac$
(10) $R^1 = R^2 = R^3 = R^5 = R^6 = R^8 = H, R^4 = R^7 = OH$
(11) $R^1 = R^2 = R^6 = Me, R^3 = Z, R^4 = R^7 = OCH_2Ph, R^5 = Ac, R^8 = H$
(12) $R^1 = R^2 = R^6 = Me, R^3 = R^5 = R^8 = H, R^4 = R^7 = OH$



(17) $R^1 = R^3 = R^7 = OH, R^2 = R^6 = H, R^4 = Ac, R^5 = Me$
(18) $R^1 = R^6 = H, R^2 = R^3 = R^7 = OH, R^4 = Ac, R^5 = Me$
(19) $R^1 = OMe, R^2 = R^6 = H, R^3 = R^7 = OH, R^4 = Ac, R^5 = Me$
(20) $R^1 = R^6 = H, R^2 = OMe, R^3 = R^7 = OH, R^4 = Ac, R^5 = Me$
(21) $R^1 = OMe, R^2 = R^6 = H, R^3 = R^7 = OCH_2Ph, R^4 = Ac, R^5 = Me$
(22) $R^1 = R^6 = H, R^2 = OMe, R^3 = R^7 = OCH_2Ph, R^4 = Ac, R^5 = Me$
(23) $R^1 = OAc, R^2 = R^6 = H, R^3 = R^7 = OCH_2Ph, R^4 = Ac, R^5 = Me$
(24) $R^1 = R^6 = H, R^2 = OAc, R^3 = R^7 = OCH_2Ph, R^4 = Ac, R^5 = Me$
(25) $R^1 = R^6 = H, R^2 = Cl, R^3 = R^7 = OCH_2Ph, R^4 = Ac, R^5 = Me$
(26) $R^1 = OMe, R^2 = R^5 = R^7 = H, R^3 = R^6 = OH, R^4 = Ac$
(27) $R^1 = OMe, R^2 = R^5 = R^7 = H, R^3 = R^6 = OCH_2Ph, R^4 = Ac$
(28) $R^1 = R^5 = R^7 = H, R^2 = OAc, R^3 = R^6 = OCH_2Ph, R^4 = Ac$
(29) $R^1 = OAc, R^2 = R^5 = R^7 = H, R^3 = R^6 = OCH_2Ph, R^4 = Ac$
(30) $R^1 = R^5 = R^7 = H, R^2 = Cl, R^3 = R^6 = OCH_2Ph, R^4 = Ac$
(31) $R^1 = R^7 = H, R^2 = OMe, R^3 = OH, R^4 = Ac, R^5 = Me, R^6 = OCH_2Ph$
(32) $R^1 = OMe, R^2 = R^7 = H, R^3 = OH, R^4 = Ac, R^5 = Me, R^6 = OCH_2Ph$
(33) $R^1 = R^7 = H, R^2 = OMe, R^3 = R^6 = OCH_2Ph, R^4 = Ac, R^5 = Me$
(34) $R^1 = OMe, R^2 = R^7 = H, R^3 = R^6 = OCH_2Ph, R^4 = Ac, R^5 = Me$
(35) $R^1 = R^5 = R^7 = H, R^2 = OMe, R^3 = R^6 = OCH_2Ph, R^4 = Ac$
(36) $R^1 = R^7 = H, R^2 = OAc, R^3 = R^6 = OCH_2Ph, R^4 = Ac, R^5 = Me$
(37) $R^1 = OAc, R^2 = R^7 = H, R^3 = R^6 = OCH_2Ph, R^4 = Ac, R^5 = Me$
(38) $R^1 = R^7 = H, R^2 = Cl, R^3 = R^6 = OCH_2Ph, R^4 = Ac, R^5 = Me$



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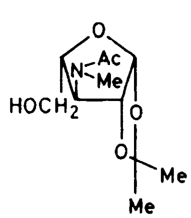
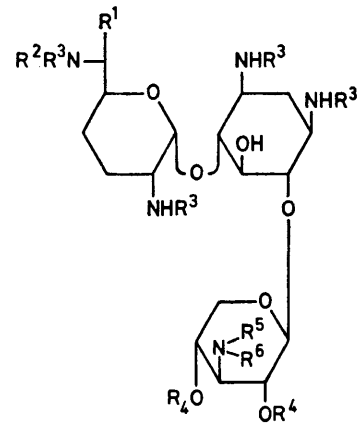
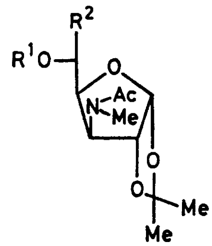


(14)

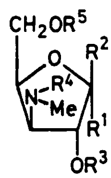
agreement with an α-glycoside. The ^{1}H n.m.r. spectrum of (10) revealed 1″-H as a doublet at δ_H 5.07 with $J_{1eq'',2ax''}$ 3.5 Hz consistent with the above assignment. The ^{13}C n.m.r. spectrum (Table 2) revealed a signal at δ_C 100.6 consistent with an α-glycoside and showed that the glycoside was indeed (1 ⟶ 6) linked. The final product isolated was *O*-3-amino-3-deoxy-β-D-xylopyranosyl-(1 ⟶ 5)-gentamine C_{1a} (44) which also showed a low positive rotation in accord with a β-glycoside. The ^{1}H n.m.r. spectrum of (44) revealed 1″-H as a doublet at δ_H 4.75 with $J_{1ax'',2ax''}$ 7.5 Hz, while the ^{13}C n.m.r. spectrum (Table 2) showed a signal at δ_C 104.5 due to C-1″, clearly supporting the β-glycosidic linkage. The ^{13}C n.m.r. data also indicated a (1 ⟶ 5) linkage to



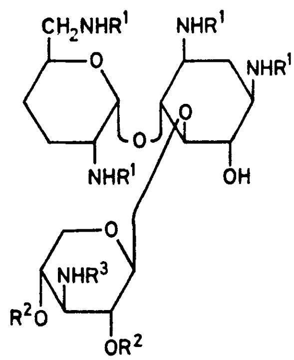
(39) $R^1 = R^2 = R^6 = H$, $R^3 = Z$, $R^4 = CH_2Ph$, $R^5 = Ac$
(40) $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$
(41) $R^1 = R^2 = R^6 = Me$, $R^3 = Z$, $R^4 = CH_2Ph$, $R^5 = Ac$
(42) $R^1 = R^2 = R^6 = Me$, $R^3 = R^4 = R^5 = H$



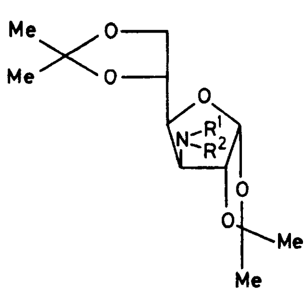
(47) $R^1 = H$, $R^2 = CH_2OH$
(48) $R^1 = R^2 = H$
(49) $R^1 = CH_2Ph$, $R^2 = H$



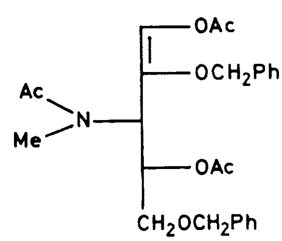
(50) $R^1 = OMe$, $R^2 = R^3 = R^4 = H$, $R^5 = CH_2Ph$
(51) $R^1 = R^3 = R^4 = H$, $R^2 = OMe$, $R^5 = CH_2Ph$
(52) $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = Ac$, $R^5 = CH_2Ph$
(53) $R^1 = R^3 = H$, $R^2 = OMe$, $R^4 = Ac$, $R^5 = CH_2Ph$
(54) $R^1 = OMe$, $R^2 = H$, $R^3 = R^5 = CH_2Ph$, $R^4 = Ac$
(55) $R^1 = H$, $R^2 = OMe$, $R^3 = R^5 = CH_2Ph$, $R^4 = Ac$
(56) $R^1 = OAc$, $R^2 = H$, $R^3 = R^5 = CH_2Ph$, $R^4 = Ac$
(57) $R^1 = H$, $R^2 = OAc$, $R^3 = R^5 = CH_2Ph$, $R^4 = Ac$
(58) $R^1 = Cl$, $R^2 = H$, $R^3 = R^5 = CH_2Ph$, $R^4 = Ac$
(59) $R^1 = H$, $R^2 = Cl$, $R^3 = R^5 = CH_2Ph$, $R^4 = Ac$



(43) $R^1 = Z$, $R^2 = CH_2Ph$, $R^3 = Ac$
(44) $R^1 = R^2 = R^3 = H$



(45) $R^1 = Ac$, $R^2 = H$
(46) $R^1 = Ac$, $R^2 = Me$



(60)

TABLE 1

Mass-spectral fragment ions [*m*/*e* (%)]

Compound	$M+1^+$	$M^{+\cdot}$	A_1	A_3	A_4	A_5	A_6	A_7	A_8	A_9	A_{10}	A_{11}
(7)	436(0.5)	435(0.5)	319(1)	291(5)	273(4)	336(5)	318(1)	308(22)	290(20)	191(40)	173(19)	163(45)
(10)	422(1)	421(0.5)	319(1)	291(0.5)	273(4)	322(7)	304(6)	294(46)	276(50)	191(60)	173(15)	163(50)
(40)	422(2)	421(0.5)	319(1)	291(0.5)	273(4)	322(3)	304(4)	294(35)	276(39)	191(52)	173(12)	163(67)
(44)	422(0.5)	421(0.5)	319(0.5)	291(0.5)	273(2)	322(6)	304(1)	294(39)	276(43)	191(66)	173(19)	163(78)
(12)	464(0.2)	463(0.5)	347(3)	319(0.5)	301(3)	336(3)	318(3)	308(9)	290(17)	191(14)	173(14)	163(13)
(42)	464(1)	463(2)	347(8)	319(4)	301(2)	336(2)	318(2)	308(7)	290(12)	191(12)	173(10)	163(12)
(62)	464(2)	463(1)	347(3)	319(5)	301(2)	336(2)	318(2)	308(7)	290(11)	191(15)	173(14)	163(26)
(64)	464(3)	463(1)	347(4)	319(60)	301(3)	336(3)	318(4)	308(7)	290(13)	191(13)	173(19)	163(20)
(70)	451(0.5)	450(0.5)	347(2)	319(1)	301(2)	323(2)	305(3)	295(8)	277(20)	191(21)	173(9)	163(23)
(74)	451(3)	450(2)	347(5)	319(2)	301(2)	323(4)	305(7)	295(16)	277(45)	191(40)	173(20)	163(40)
(72)	451(0.5)	450(0.5)	347(4)	319(2)	301(2)	323(4)	305(4)	295(6)	277(29)	191(24)	173(19)	163(28)
(79)	451(1)	450(0.8)	347(2)	319(0.5)	301(0.5)	323(2)	305(5)	295(8)	277(26)	191(18)	173(9)	163(19)
Compound	A_{12}	B_1	C_1	D_1	D_2	D_7	D_8	D_{12}	E_1	E_3	F_1	F_2
(7)	145(72)	129(90)	146(100)	418(1)	273(4)				374(0.5)	332(4)	258(6)	275(3)
(10)	145(100)	129(90)	132(25)	404(2)	273(4)					332(6)	258(12)	261(5)
(40)	145(62)	129(100)	132(16)	404(2)	273(4)					332(2)	258(14)	261(3)
(44)	145(75)	129(100)	132(19)	404(2)	273(2)					332(3)	258(3)	261(2)
(12)	145(24)	157(100)	146(83)	446(0.5)	273(6)	406(11)	261(4)		402(0.5)	360(3)	286(19)	275(10)
(42)	145(19)	157(100)	146(74)	446(0.5)	273(4)	406(7)	261(0.5)		402(2)	360(5)	286(19)	275(4)
(62)	145(46)	157(100)	146(46)	446(0.5)	273(6)	406(6)	261(7)	432(1)		360(5)	286(8)	275(5)
(64)	145(50)	157(100)	146(49)	446(0.5)	273(8)	406(3)	261(5)	432(2)		360(11)	286(6)	275(6)
(70)	145(32)	157(100)	133(5)	433(0.3)		393(6)		419(0.5)			286(12)	262(13)
(74)	145(40)	157(100)	133(20)	433(1)		393(15)		419(3)			286(40)	262(20)
(72)	145(70)	157(100)	133(10)	433(0.5)		393(11)		419(0.5)			286(1)	262(4)
(79)	145(28)	157(59)	133(5)	433(0.5)		393(3)					286(8)	262(6)

the deoxystreptamine ring (Table 3). The mass-spectral data for (40), (10), and (44) are given in Table 1.

The synthesis of D-xylofuranosyl analogues was carried out as follows. 3-Acetamido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (45) [15-17] on treatment with sodium hydride and methyl iodide gave the *N*-methyl derivative (46), which on hydrolysis with aqueous acetic acid afforded the 1,2-*O*-isopropylidene derivative (47). Periodate cleavage of the glycol (47) gave 3-deoxy-1,2-*O*-isopropylidene-3-*N*-methylacetamido-α-D-xylofuranose (48), which was then converted into the 5-*O*-benzyl derivative (49). The latter on aqueous acidic hydrolysis followed by methanolysis gave methyl 5-*O*-benzyl-3-deoxy-3-methylamino-α- and -β-D-xylofuranoside (50) and (51). No attempt was made to isolate minor products of the reaction. The mass

TABLE 2

^{13}C N.m.r. chemical shifts (δ_C p.p.m. downfield from tetramethylsilane in D_2O)

Carbon	(7)	(7)H⁺	$\Delta\delta_C$(Base→H⁺)	(10)	(10)H⁺	$\Delta\delta_C$(Base→H⁺)	(40)	(40)H⁺	$\Delta\delta_C$(Base→H⁺)	(44)	(44)H⁺	$\Delta\delta_C$(Base→H⁺)
C-1	51.4	50.4	−1.0	51.4	50.5	−0.9	49.7	49.1	−0.6	51.1 *a*	50.4	−0.7
C-2	36.4	28.4	−8.0	36.5	28.4	−8.1	36.3	28.6	−7.7	36.4	28.6	−7.8
C-3	50.6 *a*	49.5 *a*	−1.1	50.6 *a*	49.4	−1.2	50.6 *a*	49.5	−1.1	51.4 *a*	49.4 *a*	−2.0
C-4	88.7	77.6	−11.1	88.2	77.3	−10.9	88.3	77.0	−11.3	87.0	76.2	−10.8
C-5	75.3	75.1	−0.2	75.2	75.1	−0.1	76.6	75.3	−1.3	82.6	82.6	0
C-6	87.8	84.4	−3.4	87.6	84.5	−3.1	87.4	80.6	−6.8	79.0	73.7	−5.3
C-1′	101.9	95.8	−6.1	101.7	95.6	−6.1	102.1	95.5	−6.6	102.7	95.7	−7.0
C-2′	50.3 *a*	49.3 *a*	−1.0	50.4 *a*	49.4	−1.0	50.2 *a*	49.5	−0.7	50.9 *a*	49.3 *a*	−1.6
C-3′	26.6	21.1	−5.5	26.6	21.2	−5.4	26.7	21.2	−5.5	25.9	21.2	−4.7
C-4′	28.1	26.0	−2.1	28.1	26.1	−2.0	28.2	26.2	−2.0	28.0	25.6	−2.4
C-5′	71.1	66.7	−4.4	70.9	66.8	−4.1	71.1	66.8	−4.3	70.2	66.8	−3.4
C-6′	45.6	43.3	−2.3	45.6	43.4	−2.2	45.8	43.5	−2.3	45.6	43.2	−2.4
C-7′												
6′-NCH₃												
C-1″	101.1	102.1	+1.0	100.6	101.4	+0.8	105.3	104.2	−1.1	104.5	104.6	−0.1
C-2″	68.6	66.1	−2.5	72.6	68.8	−3.8	74.5	70.1	−4.4	74.5	70.0	−4.5
C-3″	59.2	58.9	−0.3	55.4	55.9	+0.5	58.9	58.6	−0.3	58.8	58.5	−0.3
C-4″	64.6	63.1	−1.5	70.2	66.2	−4.0	70.1	66.9	−3.2	70.2	67.0	−3.2
C-5″	65.4	64.8	−0.6	62.8	63.2	+0.4	67.4	66.5	−0.9	67.1	66.3	−0.8
3″-NCH₃	32.6	30.7	−1.9									
Carbon	**(12)**	**(12)H⁺**	**$\Delta\delta_C$(Base→H⁺)**	**(42)**	**(42)H⁺**	**$\Delta\delta_C$(Base→H⁺)**	**(62)**	**(62)H⁺**	**$\Delta\delta_C$(Base→H⁺)**	**(64)**	**(64)H⁺**	**$\Delta\delta_C$(Base→H⁺**
C-1	51.5	50.4	−1.1	49.6	49.4	−0.2	50.8 *a*	50.0	−0.8	50.9	50.7	−0.2
C-2	36.5	28.4	−8.1	36.3	28.6	−7.7	36.7	28.7	−8.0	36.5	28.4	−8.1
C-3	50.5 *a*	49.5	−1.0	50.2 *a*	49.6	−0.6	50.5 *a*	49.5	−1.0	50.9	49.7 *a*	−1.2
C-4	88.3	77.3	−11.0	88.2	77.3	−10.9	88.0	77.3	−10.7	86.0	76.2	−9.8
C-5	75.1	75.2	0.1	76.5	75.4	−1.1	75.5	75.1	−0.4	85.5	84.5	−1.0
C-6	88.0	84.6	−3.4	87.7	80.6	−7.1	87.6	82.1	−5.5	77.5	72.4	−5.1
C-1′	102.6	95.9	−6.7	102.5	96.1	−6.4	102.4	95.9	−6.5	101.1	95.2	−5.9
C-2′	50.8 *a*	49.4	−1.4	50.7 *a*	49.1	−1.6	50.8 *a*	49.5	−1.3	50.9	49.2 *a*	−1.7
C-3′	26.9	21.3	−5.6	26.8	21.3	−5.5	26.7	21.3	−5.4	27.3	21.4	−5.9
C-4′	25.7	23.2	−2.5	25.6	23.2	−2.4	25.7	23.4	−2.3	25.1	22.6	−2.5
C-5′	72.8	70.1	−2.7	72.6	70.1	−2.5	72.4	70.0	−2.4	72.6	71.7	−0.9
C-6′	58.0	58.5	+0.5	58.0	58.5	+0.5	58.1	58.5	+0.4	58.0	58.4	+0.4
C-7′	14.5	10.8	−3.7	14.3	10.9	−3.4	14.3	10.8	−3.5	14.1	11.0	−3.1
6′-NCH₃	33.3	32.0	−1.3	33.1	32.0	−1.1	33.2	32.1	−1.1	33.1	32.0	−1.1
C-1″	100.8	101.6	+0.8	105.4	104.4	−1.0	103.8	103.0	−0.8	103.3	101.8	−1.5
C-2″	70.8	67.1	−3.7	72.3	68.5	−3.8	76.8	74.5	−2.3	76.3	74.3	−2.0
C-3″	62.7	61.5	−1.2	65.8	64.7	−1.1	64.4	63.3	−1.1	64.7	63.7	−1.0
C-4″	68.7	64.3	−4.4	68.3	64.5	−3.8	78.8	76.6	−2.2	78.7	76.5	−2.2
C-5″	63.0	63.3	+0.3	66.4	66.9	+0.5	61.6	60.4	−1.2	61.5	60.3	−1.2
3″-NCH₃	34.2	30.5	−3.7	33.8	31.3	−2.7	34.8	33.9	−0.9	34.7	33.8	−0.9

a May be interchanged in any vertical column.

spectra of (50) and (51) revealed characteristic fragment ions at *m/e* 236 (*b*), 176 (*e*), and 146 (*f*) (Figure 1). The rotations and ^{1}H n.m.r. spectra were in accord with the assigned anomeric configurations. *N*-Acetylation of

TABLE 3

Linkage determination by g.l.c.–mass spectroscopy

Derivative	Fragments (*m/e*) *j*	*k*	*l*	*m*
Reference (73)	254	187		
Reference (74)			196	129
(70) ⟶ (73)	254	187		
(72) ⟶ (73)	254	187		
(79) ⟶ (73)	254	187		

(50) and (51) gave (52) and (53) respectively. The above reaction sequence was scaled up and the intermediate amines (50) and (51) were directly *N*-acetylated prior to chromatography to give (52) and (53). The furanosides (52) and (53) could only be partially separated by chromatography to give samples that were identical with those prepared above from pure (50) and (51) by *N*-acetylation. The bulk of the material was obtained as an overlap cut. The ^{1}H n.m.r. spectrum revealed signals at δ_H 2.12 due to the 3-NAc groups and at δ_H 3.06 and 3.12 due to the 3-N(Ac)CH_3 groups of

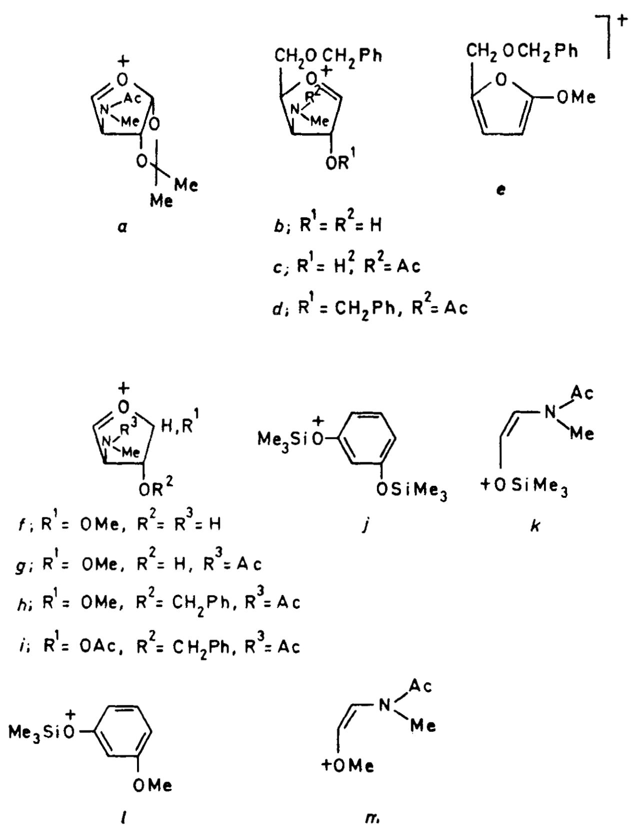
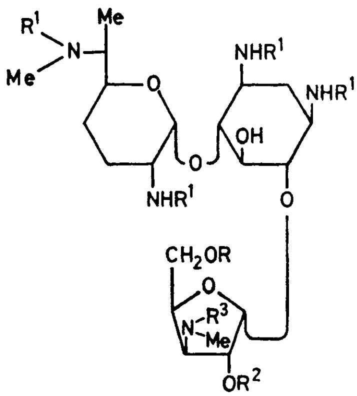


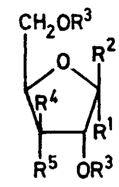
FIGURE 1 Mass-spectral fragment ions

methyl 4-*O*-benzyl-3-deoxy-3-methylacetamido-α- and -β-D-xylopyranoside (31) and (32). The pyranosides were present to the extent of 25—30% and appear to be forming by migration of the 5-*O*-benzyl group during the acidic hydrolysis.[1] The mixture was benzylated to give a mixture of methyl 2,5-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-D-xylofuranoside (54) and (55), and methyl 2,4-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-D-xylopyranoside (33) and (34). Acetolysis of the above mixture as described earlier gave 1-*O*-acetyl-2,5-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-D-xylofuranose (56) and (57), which could be separated from 1-*O*-acetyl-2,4-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-D-xylopyranose (36) and (37) by column chromatography. 1,4-Di-*O*-acetyl-2,5-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-D-*threo*-pent-1-enose (60) was also formed as a by-product of the reaction.[1] The 1-*O*-acetyl pyranosides (36) and (37) were also prepared by *N*-methylation of (35) and (27) followed by acetolysis. Treatment of (36) and (37) with acetyl chloride in the presence of dry hydrogen chloride afforded 2,4-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α-D-xylopyranosyl chloride (38). The latter was condensed with 1,3,2′,6′-tetrakis-*N*-benzyloxycarbonylgentamine C_1 (3) in the presence of silver toluene-*p*-sulphonate to give a mixture of pseudotrisaccharides (41) and (11), which could not be separated. The mixture was treated with sodium in liquid ammonia and then subjected to basic hydrolysis to give two products. The first, *O*-3-deoxy-3-methylamino-β-D-xylopyranosyl-(1 ⟶ 6)-gentamine C_1 (42) showed a low positive rotation and revealed a signal in the ^{1}H n.m.r. spectrum at δ_H 4.60 with $J_{1ax'',2ax''}$ 8 Hz due to 1″-H, consistent with values expected for a β-glycoside. The occurrence of the anomeric carbon (C-1″) at δ_C 105.4 in the ^{13}C n.m.r. spectrum (Table 2) confirmed this assignment. The ^{13}C n.m.r. data indicated that the glycoside was (1 ⟶ 6) linked. The second product, *O*-3-deoxy-3-methylamino-α-D-xylopyranosyl-(1 ⟶ 6)-gentamine C_1 (12) showed a high positive rotation and revealed a signal at δ_H 5.03 in the ^{1}H n.m.r. spectrum having $J_{1eq'',2ax''}$ 3.5 Hz due to 1″-H, consistent with the values expected for an α-glycoside. A signal at δ_C 100.8 in the ^{13}C n.m.r. spectrum (Table 2) due to the anomeric carbon (C-1″) confirmed this assignment. The ^{13}C n.m.r. data also indicated that the glycoside was (1 ⟶ 6) linked. The mass spectral data for (12) and (42) are given in Table 1. The 1-*O*-acetyl furanoses (56) and (57) were treated with acetyl chloride in the presence of dry hydrogen chloride to give 2,5-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-D-xylofuranosyl chloride (58) and (59). The latter were condensed with 1,3,2′,6′-tetrakis-*N*-benzyloxycarbonylgentamine C_1 (3) in the presence of silver toluene-*p*-sulphonate to give a mixture of two protected pseudotrisaccharides (61) and (63) which could not be separated by chromatography. The mixture was treated with sodium in liquid ammonia and then subjected to basic hydrolysis to give two products. The first, *O*-3-deoxy-3-methylamino-α-D-xylofuranosyl-(1 ⟶ 5)-gentamine C_1 (64) showed a moderately high positive rotation, although not as high as that observed for (1 ⟶ 6) linked α-glycosides. The anomeric proton

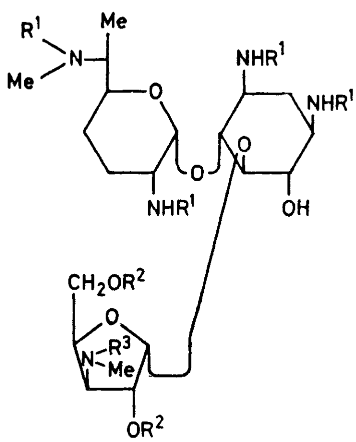
1″-H occurred at δ_H 4.17 in the ^{1}H n.m.r. spectrum and exhibited $J_{1'',2''}$ 4.5 Hz consistent with an α-glycosidic linkage. The ^{13}C n.m.r. spectrum (Table 2) revealed a signal at δ_C 103.3 due to C-1″ consistent with an α-glycoside and clearly indicated that the glycoside was (1 → 5) linked. The second product, *O*-3-deoxy-3-methylamino-α-D-xylofuranosyl-(1 → 6)-gentamine (62) showed the expected high positive rotation and also showed a low-amplitude c.d. extremum at 278 nm in TACu consistent with a (1 → 6) linked α-glycoside. The ^{1}H n.m.r. spectrum revealed 1″-H as a doublet at δ_H 5.20 having $J_{1'',2''}$ 4.5 Hz, consistent with an α-glycoside. The ^{13}C n.m.r. spectrum (Table 2) revealed a signal at δ_C 103.8 due to C-1″ consistent with an α-glycoside and also demonstrated that the glycoside was (1 → 6) linked. The mass spectral data for (64) and (62) are given in Table 1.



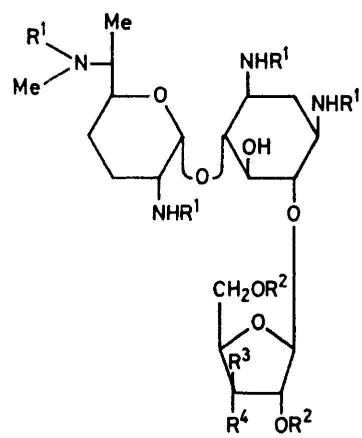
(61) R^1 = Z, R^2 = CH_2Ph, R^3 = Ac
(62) R^1 = R^2 = R^3 = H



(65) R^1 = Br, R^2 = R^5 = H, R^3 = Ac, R^4 = OAc
(66) R^1 = R^5 = H, R^2 = Br, R^3 = Ac, R^4 = OAc
(67) R^1 = Br, R^2 = R^4 = H, R^3 = Bz, R^5 = OBz
(68) R^1 = R^4 = H, R^2 = Br, R^3 = Bz, R^5 = OBz



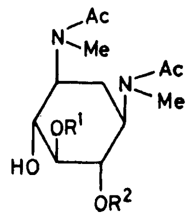
(63) R^1 = Z, R^2 = CH_2Ph, R^3 = Ac
(64) R^1 = R^2 = R^3 = H



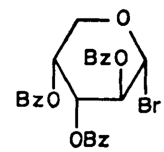
(69) R^1 = Z, R^2 = Ac, R^3 = OAc, R^4 = H
(70) R^1 = R^2 = R^4 = H, R^3 = OH
(71) R^1 = Z, R^2 = Bz, R^3 = H, R^4 = OBz
(72) R^1 = R^2 = R^3 = H, R^4 = OH

A series of neutral glycosyl derivatives of gentamine was prepared in the following manner. 2,3,5-Tri-*O*-acetyl-α- and -β-xylofuranosyl bromide (65) and (66) [18] were condensed with 1,3,2′,6′-tetrakis-*N*-benzyloxycarbonylgentamine C_1 (3) in the presence of mercury(II) cyanide and calcium sulphate to give, as the principal product of the reaction, *O*-2,3,5-tri-*O*-acetyl-β-D-xylofuranosyl-(1 → 6)-1,3,2′,6′-tetrakis-*N*-benzyloxycarbonylgentamine C_1 (69). Ammonolysis followed by reduction with sodium in liquid ammonia afforded *O*-β-D-xylofuranosyl-(1 → 6)-gentamine C_1 (70). The ^{1}H n.m.r. spectrum of (70) revealed a singlet at δ_H 5.32 due to 1″-H, consistent with the presence of a β-glycoside. The mass spectrum is given in Table 1. The linkage was proved by *N*-acetylation, *NO*-methylation, and acidic hydrolysis to give 1,3-di-*N*-acetyl-1,3-di-*N*-methyl-5-*O*-methyl-2-deoxystreptamine (73) which was subjected to g.l.c.–mass spectral analysis [1] revealing the presence of strong ions at *m/e* 254 (*j*) and 187 (*k*) (Table 3) (Figure 1) consistent with a (1 → 6) linkage.[1]

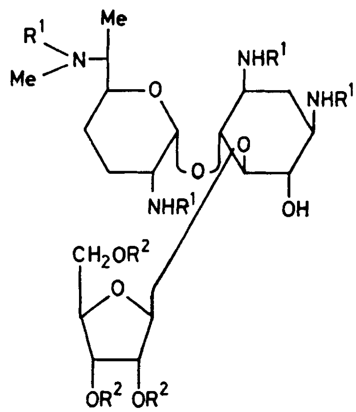
Condensation of 2,3,5-tri-*O*-benzoyl-α- and -β-D-ribofuranosyl bromide (67) and (68)[19] with 1,3,2′,6′-tetrakis-*N*-benzyloxycarbonylgentamine C_1 (3) in the presence of mercury(II) cyanide and calcium sulphate afforded *O*-2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-(1 ⟶ 6)-1,3,2′,6′-tetrakis-*N*-benzyloxycarbonylgentamine C_1 (71) as the major product (74%) and *O*-2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-(1 ⟶ 5)-1,3,2′,6′-tetrakis-



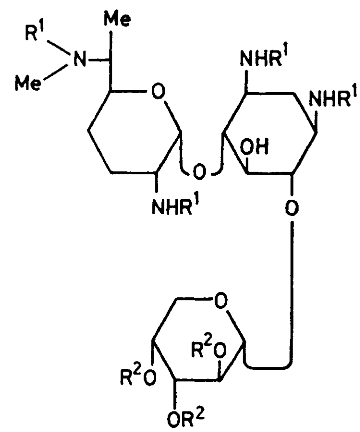
(73) R¹=Me, R²=H
(74) R¹=H, R²=Me



(77)



(75) R¹=Z, R²=Bz
(76) R¹=R²=H



(78) R¹=Z, R²=Bz
(79) R¹=R²=H

N-benzyloxycarbonylgentamine C_1 (75) as the minor product (11%). Deprotection of (71) by ammonolysis followed by reduction with sodium in liquid ammonia gave *O*-β-D-ribofuranosyl-(1 ⟶ 6)-gentamine C_1 (72). The ^{1}H n.m.r. spectrum of (72) revealed a singlet at δ_H 5.37 due to 1″-H, consistent with a β-glycoside. The linkage was shown to be (1 ⟶ 6) by g.l.c.–mass spectroscopy[1] (Table 3) (Figure 1) as fragment ions *i* and *k* were observed. Deprotection of (73), as described above, gave *O*-β-D-ribofuranosyl-(1 ⟶ 5)-gentamine C_1 (76) which exhibited a singlet at δ_H 5.40 in the ^{1}H n.m.r. spectrum due to 1″-H, consistent with a β-glycoside. Having proved the linkage of (72) it followed that (74) was the (1 ⟶ 5)-linked product. The mass-spectral data for (72) and (76) are given in Table 1.

When 2,3,4-tri-*O*-benzoyl-α-D-arabinopyranosyl bromide (77)[20] was condensed with 1,3,2′,6′-tetra-*N*-benzyloxycarbonylgentamine C_1 (3) in the presence of mercury(II) cyanide and Drierite, *O*-2,3,4-tri-*O*-benzoyl-α-D-arabinopyranosyl-(1 ⟶ 6)-1,3,2′,6′-tetra-*N*-benzyloxycarbonylgentamine C_1 (78) was obtained. Deprotection of (78) by ammonolysis followed by reduction with sodium in liquid ammonia gave *O*-α-D-arabinopyranosyl-(1 ⟶ 6)-gentamine C_1 (79). The ^{1}H n.m.r. spectrum of (79) exhibited a doublet at δ_H 4.54 due to 1″-H having $J_{1ax'',2ax''}$ 6 Hz, consistent with the presence of an α-glycoside. The linkage was shown to be (1 ⟶ 6) by g.l.c.–mass spectroscopy[1] (Table 3) (Figure 1) because of the formation of (73) which gave fragment ions *j* and *k* in the mass spectrum. The mass-spectral data for (79) are given in Table 1.

In all the above as well as earlier condensations[1] with gentamine we have observed that when both the 5- and 6-hydroxy-groups are available for glycosylation, reaction occurs predominantly at the 6-hydroxy-group.[1]

The solution conformations of these novel semi-synthetic aminoglycoside antibacterials were of considerable interest to us for the reasons stated earlier.[1] The ^{13}C n.m.r. chemical shifts for eight of the compounds prepared in this study are given in Table 2. The $\Delta\delta_C$ values in going from 2-deoxystreptamine to the appropriate trisaccharide are given in Table 4. It is evident from the $\Delta\delta_C$ values that the aminoglycosides which contain 6-*O*-β-L-glycosyl units, namely (7), or 6-*O*-α-D-glycosyl units, namely (10), (12), and (62), adopt the usual rotamer *a* (Figure 2) about the C-4-*O* glycosidic bond resulting in shielding at C-3, and the usual rotamer *b* about the C-6-*O* glycosidic bond resulting in shielding of C-5.[1,6,21-24] Both rotamers *a* and *b* satisfy the requirements of the *exo*-anomeric effect.[25-29] Somewhat greater shielding than usual (—0.1 to —0.5) was observed at C-1 (—0.8) in (62). Similar observations have been made with some 4-*O*-β-D-glycosyl derivatives of garamine [23,24] in which C-3 experiences some shielding, and Rotamer *c* would be expected to produce significant shielding of C-6 owing to the 1,3-diaxial interaction between the ring oxygen of the 6-*O*-glycoside and 6*ax*-H. Such shielding at C-6 has been observed in semisynthetic aminoglycoside antibacterials having 1-*epi* or no substituents at all, at C-1.[30] Owing to the absence of an equatorial hydrogen at C_1 in (62), less pronounced

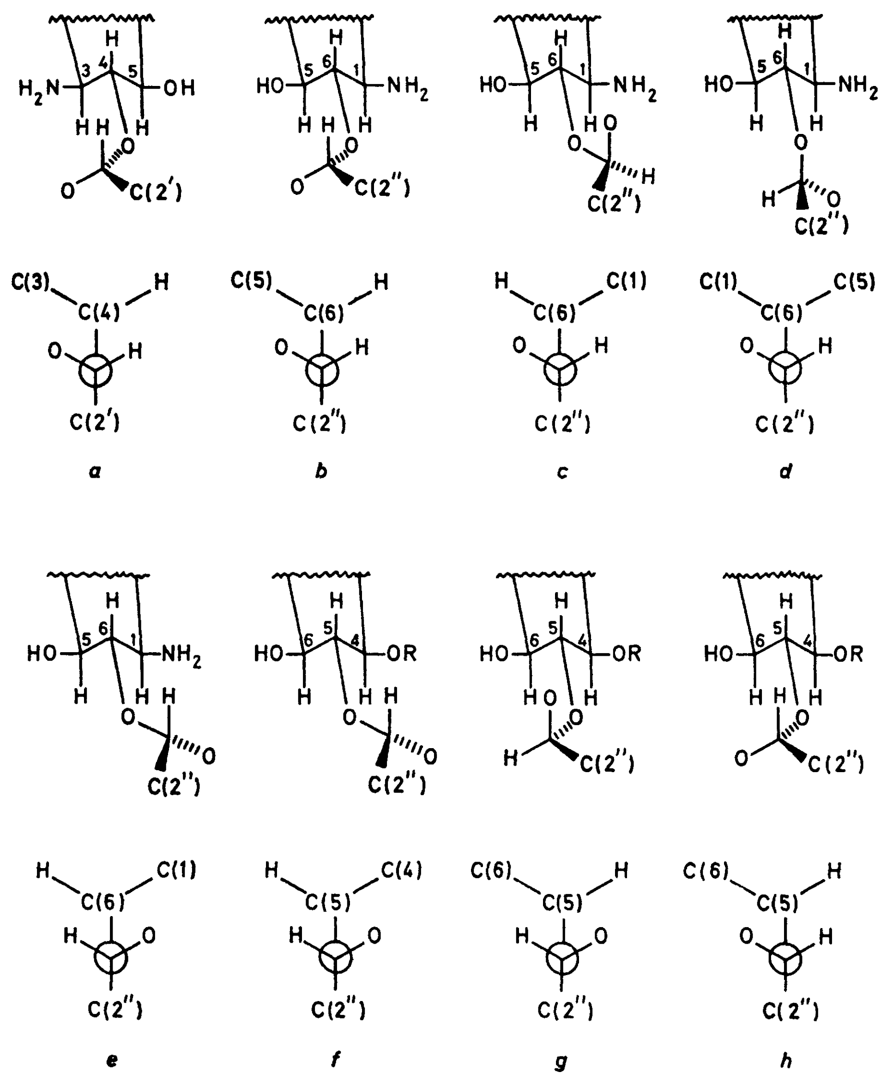


FIGURE 2 Rotamers about the glycosidic linkages

with some 6-*O*-α-D-glycosyl derivatives of gentamine [1] such as (62) in which C-1 experiences shielding. We will illustrate our arguments with reference to rotamers about the C-6-*O* glycosidic bond for (62). Analogous arguments apply to the alternative rotamers about the C-4–*O* glycosidic bond.[23,24] The possibility that the shielding at C-1 might arise as a result of the presence of alternative rotamers, in addition to rotamer *b*, was excluded for the following reasons. The only other rotamers that need be considered are rotamers *c* and *d*, as all other possible rotamers would exhibit chemical shifts intermediate between those of rotamers *b*, *c*, and *d*. shielding would be expected at C-1 or C-1″ in rotamer *c* in (62), if this rotamer was indeed present. In the case of the 1-deamino- and 1-*epi*-derivatives, however, steric interaction between the equatorial proton at C-1 and 1″-H (Figure 3) would be predicted [31] and indeed does produce, pronounced shielding of C-1 and C-1″ as well.[30] No shieldings of C-6 or C-1″ were observed in (62) (Table 2) relative to other aminoglycosides that exist as rotamer *b*. The only additional shielding observed was at C-1 (—0.8). Rotamer *d* on the other hand, would be expected to produce significant shielding of C-5 and C-1″ owing to steric interaction between 5*ax*-H and

1*eq*″-H of the general type shown in Figure 3.[30] The ring oxygen of the 6-*O*-glycoside would also undergo the formal equivalent of a 1,3-interaction with the axial proton on C-1 which would result in marked shielding at C-1. This was not in accord with the observed facts

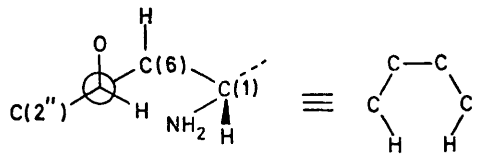


FIGURE 3 Non-bonded hydrogen interaction

(Tables 2 and 4). Both rotamers *c* and *d* would also satisfy the requirements of the *exo*-anomeric effect.[25-29] The origin of the shielding at C-1 in (62) remains uncertain.

The 6-*O*-β-D-glycosyl derivatives (40) and (42) exhibited $\Delta\delta_C$ values (Table 4) that indicated the presence of the rotamer *a* about the C-4–*O* glycosidic bond as evidenced by the shielding of C-3. No shielding was observed at C-5. However, shielding was observed presence of rotamer *f* about the C-5–*O* glycosidic bond. However, the reduced deshielding at C-5 (+5.8), indicating a strong shielding interaction, precludes rotamer *f*. We therefore conclude that the 5-*O*-glycoside adopts rotamer *g* about the C-5–*O* glycosidic bond. The 1,3-interaction[33-35] between the ring oxygen of the 5-*O*-glycoside and 5*ax*-H would be expected to produce strong shielding at C-5[30] which was indeed observed. No shielding would be expected at C-4 and little if any shielding would be expected at C-6 and C-1″ as the equatorial 6-hydroxy-group would preclude any non-bonded hydrogen interactions with 1*eq*″-H.[30,31] Rotamer *g* would also satisfy the requirements of the *exo*-anomeric effect.[25-29] The reason why this 4,5-*O*-glycosyl aminoglycoside adopts rotamer *g* rather than rotamer *f* is almost certainly because of the severe dipole–dipole interaction between the oxygen of the C-4–*O* glycosidic bond and the ring oxygen of the 5-*O*-glycoside, which is relieved in rotamer *g*.

The $\Delta\delta_C$ values in going from 2-deoxystreptamine[21] to the 5-*O*-α-D-xylofuranosyl analogue (64) are also given in Table 4. In this case no significant reduction in the

TABLE 4

$\Delta\delta_C$ Values for DOS[21] ⟶ trisaccharide

Carbon	(7)	(10)	(12)	(62)	(40)	(42)	(44)	(64)
C-1	−0.2	−0.2	−0.1	−0.8	−1.9	−2.0	−0.5	−0.7
C-2	−0.6	−0.5	−0.5	−0.3	−0.7	−0.7	−0.6	−0.5
C-3	−1.0	−1.0	−1.1	−1.1	−1.0	−1.4	−0.2	−0.7
C-4	+10.2	+9.7	+9.8	+9.5	+9.8	+9.7	+8.5	+7.5
C-5	−1.3	−1.4	−1.5	−1.1	0	−0.1	+6.0	+8.9
C-6	+9.3	+9.1	+9.5	+9.1	+8.9	+9.2	+0.5	−1.0

instead at C-1 indicating that rotamer *e* is the preferred rotamer about the C-6–*O* glycosidic bond in the 6-*O*-β-D-glycosyl derivatives as was observed earlier.[1] Rotamer *e* also satisfies the requirements of the *exo*-anomeric effect.[25-29] These results are in full agreement with those which we would have predicted based on our earlier work[23,24] on 4-*O*-β-D-glycosyl derivatives of garamine and on subsequent studies on 4-*O*-α-L-glycosyl derivatives of garamine.[32]

Only two 5-*O*-linked glycosides were isolated during the course of this work, namely (44) and (64). The $\Delta\delta_C$ values in going from 2-deoxystreptamine[21] to the 5-*O*-β-D-xylopyranosyl analogue (44) are given in Table 4. Although of limited utility in assigning glycoside rotamers owing to the 4,5-*O*-glycosyl arrangement in (44), they are instructive in that they demonstrate reduced shielding at C-3 (−0.2) relative to that observed for gentamine C_{1a} (−1.1)[21] as well as reduced deshielding (indicating a shielding component) at C-4 (+8.5) relative to gentamine C_{1a} (+9.6). This may best be explained by assuming a modest clockwise rotation about the O-4–C-4 bond in rotamer *a* for the 4-*O*-glycoside in (44). The $\Delta\delta_C$ values in going from gentamine C_{1a}[21] to (44) are given in Table 5. Slight deshielding at C-3 (+0.9) and shielding at C-4 (−1.1) and C-1″ (−0.8) was evident, indicating that some rotation about the O-4–C-4 bond is occurring in (44). The shielding at C-4 (Table 5) could have arisen from the shielding at C-3 (−0.7) relative to gentamine C_1[21] (−0.8) was observed, while reduced deshielding (indicating a shielding component) at C-4 (+7.5) relative to gentamine C_1[21] (+10.3) was evident. This is best explained by assuming a somewhat greater rotation about the O-4–C-4 bond in rotamer *a* for the 4-*O*-glycoside in (64), than was observed in the case of (44) above. This is further supported by the $\Delta\delta_C$ values in going from gentamine C_1[21] to (64) (Table 5). Thus C-3 is

TABLE 5

$\Delta\delta_C$ Values for gentamine C_{1a}(2), or C_1(1)[21] ⟶ trisaccharide

Carbon	(2) ⟶ (44)	(1) ⟶ (64)
C-1	−0.2	−0.4
C-2	−0.4	−0.3
C-3	+0.9	+0.1
C-4	−1.1	−2.8
C-5	+5.8	+8.7
C-6	+0.7	−0.9

unchanged and C-4 experiences a $\Delta\delta_C$ of −2.8. Strong deshielding is observed at C-5 (+8.7), while C-6 experiences some shielding (−0.9). The data suggest that the 5-*O*-glycoside adopts the preferred rotamer *h* about the C-5–*O* glycosidic bond. Rotamer *h* also satisfies the requirements of the *exo*-anomeric effect.[25-29] The only other rotamer studies that have been carried out on 4,5-*O*-glycosyl aminoglycosides were reported from these laboratories by Nagabhushan.[36]

The antibacterial activity of these novel semisynthetic aminoglycoside antibacterials will be reported elsewhere.

EXPERIMENTAL

All physical data were recorded as described in Part 7.[1]

3-*Deoxy*-1,2-O-*isopropylidene*-3-N-*methylacetamido*-β-L-*arabinofuranose* (14).—3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*N*-methylacetamido-α-D-galactofuranose (13) [13] (6.2 g) was dissolved in 50% aqueous acetic acid (170 ml) and the solution was allowed to remain at 25 °C for 6.5 h. The solution was evaporated to dryness and the residue was taken up in distilled water (75 ml). Sodium metaperiodate (6.5 g) in distilled water (150 ml) was added. The pH of the solution was adjusted to 6.5 by addition of dilute sodium hydrogen carbonate solution and after 1 h at 25 °C the solution was cooled to 4 °C and allowed to remain for a further 18 h. Ethylene glycol (1 ml) was added and the solution was allowed to warm up to 25 °C over 30 min. Methanol (950 ml) was added and the mixture was allowed to stand at 7 °C for 14 h. The precipitate was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in ethanol (160 ml) and sodium borohydride (3.1 g) was added. After 40 min at 25 °C the pH of the solution was adjusted to 8 by addition of Amberlite IR 120 (H^+) resin. The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in methanol (15 ml) and acetic anhydride (2.5 ml) was added. After 10 min at 25 °C the solution was concentrated to dryness and then co-evaporated with methanol and then toluene. The resulting gum was chromatographed on silica gel (98 × 5 cm column) using 3% v/v methanol–chloroform as the eluant to give 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*N*-methylacetamido-α-D-galactofuranose (13) (1.15 g, 19%), 3-*deoxy*-1,2-O-*isopropylidene*-3-N-*methylacetamido*-β-L-*arabinofuranose* (14) (2.03 g, 57%) as a gum (Found: C, 54.0; H, 8.0; N, 5.9. $C_{11}H_{19}NO_5$ requires C, 53.9; H, 7.8; N, 5.7%), *m/e* 245 ($M^{+\cdot}$), $[\alpha]_D^{26}$ +24.1° (MeOH), $\nu_{max.}$ (film) 3 400 and 1 640 cm^{-1}, δ_H ($CDCl_3$) * 1.36 and 1.58 [6 H, 2 s, $OC(CH_3)_2O$], 2.11br and 2.20br (3 H, 2 s, 3-NAc), 2.87br and 3.10br (3 H, 2 s, 3-NCH_3), 4.84 (1 H, d, $J_{1,2}$ 4 Hz, 2-H), and 6.02 (1 H, d, $J_{1,2}$ 4 Hz, 1-H), the *dimer* (16) (0.23 g, 6%) as a glass (Found: *m/e*, 473.2119. $C_{21}H_{33}N_2O_{10}$ requires $M - CH_3$, 473.2135), $\nu_{max.}$ ($CHCl_3$) 3 400, 1 640, and 1 030 cm^{-1}, δ_H (D_2O) * 1.37br and 1.60br [12 H, 2 s, $OC(CH_3)_2O$], 2.14br, 2.24br, and 2.27br (6 H, 3 s, NAc), 2.86, 3.08, 3.15, and 3.18 (6 H, 4 s, NCH_3), and 6.17 (2 H, overlapping doublets, 1- and 1′-H), and 3-*deoxy*-4-C-*hydroxymethyl*-1,2-O-*isopropylidene*-3-N-*methylacetamido*-β-L-threo-*pentofuranose* (15) (0.7 g, 13%) as a gum (Found: *m/e*, 260.1131. $C_{11}H_{18}NO_6$ requires $M - CH_3$, 260.1134), $[\alpha]_D^{26}$ +21.7° (MeOH), $\nu_{max.}$ ($CHCl_3$) 3 360, 1 630, and 1 060 cm^{-1}, δ_H (D_2O) * 1.40br and 1.62br (6 H, 2 s, O-C-$(CH_3)_2O$], 2.17 and 2.23 (3 H, 2 s, 3-NAc), 2.89 and 3.12 (3 H, 2 s, 3-NCH_3), 5.21 (1 H, dd, $J_{1,2}$ 4, $J_{2,3}$ 1 Hz, 2-H), and 6.19 (1 H, d, $J_{1,2}$ 4 Hz, 1-H).

3-*Deoxy*-3-N-*methylacetamido*-α- *and* -β-L-*arabinopyranose* (17) *and* (18).—3-Deoxy-1,2-*O*-isopropylidene-3-*N*-methylacetamido-β-L-arabinofuranose (14) (8.2 g) was dissolved in distilled water (100 ml). Amberlite IR 120 (H^+) resin (8 g) was added and the mixture was stirred at 25 °C for 18 h. The resin was filtered off and the filtrate was evaporated to dryness. The solid was taken up in methanol and when the volume was reduced the 3-*deoxy*-3-N-*methylacetamido*-α- and -β-L-*arabinopyranoses* (17) and (18) (5.65 g, 83%) crystallized as needles, m.p. 167—168.5 °C (Found: C, 46.6; H, 7.30; N, 7.1. $C_8H_{15}NO_5$ requires C, 46.8; H, 7.4; N, 6.8%), *m/e* 206 [$(M + 1)^+$], $[\alpha]_D^{26}$ +110.7° (MeOH), $\nu_{max.}$ (KBr) 3 300, 1 610, 1 080, and 1 015 cm^{-1}, δ_H (D_2O) 2.18 (3 H, s, 3-NAc), 3.17 (3 H, s, 3-NCH_3), and 5.30 (<1 H, unresolved m, 1*eq*-H).

Methyl 3-*Deoxy*-3-N-*methylacetamido*-α- and -β-L-*arabinopyranoside* (19) *and* (20).—3-Deoxy-3-*N*-methylacetamido-α- and -β-L-arabinopyranose (17) and (18) (6.77 g) was dissolved in 5M-hydrogen chloride in methanol (100 ml) and the mixture was heated under reflux for 43 h. The solution was evaporated to dryness *in vacuo* to remove most of the hydrogen chloride. The residue was taken up in methanol and neutralized with Amberlite IRA 401S (OH^-) resin and the resin was then filtered off. The volume of the solution was reduced to 100 ml and acetic anhydride (10 ml) was added and the mixture was allowed to remain at 25 °C for 15 min. The solution was evaporated to dryness and azeotroped with toluene to give the methyl glycosides (19) and (20) (7.2 g, 100%) as a gum. An aliquot (220 mg) of the anomeric mixture of (19) and (20) was chromatographed on a silica-gel column (58 × 1.6 cm) using 2% methanol in chloroform as the eluant to give analytical samples of the β-*anomer* (20) as needles, m.p. 139—141 °C (Found: C, 49.3; H, 7.8; N, 6.1. $C_9H_{17}NO_5$ requires C, 49.30; H, 7.8; N, 6.4%), *m/e* 220 [$(M + 1)^+$], 219 ($M^{+\cdot}$), and 188 ($M - 31$), $[\alpha]_D^{26}$ +213.7° (MeOH), $\nu_{max.}$ (Nujol) 3 330 and 1 620 cm^{-1}, δ_H (D_2O) * 2.19 (3 H, s, 3-NAc), 3.04 and 3.17 [3 H, 2 s, 3-NCH_3(Ac)], 3.48 (3 H, s, 1-OCH_3), 4.34 (1 H, dd, $J_{1,2}$ 3.5, $J_{2,3}$ 11 Hz, 2-H), and 4.94 (1 H, d, $J_{1,2}$ 3.5 Hz, 1-H) and the α-*anomer* (19) as a syrup (Found: $M^{+\cdot}$, 219.1099. $C_9H_{17}NO_5$ requires *M*, 219.1107), *m/e* 220 [$(M + 1)^+$], 219 ($M^{+\cdot}$), and 188 ($M - 31$), $[\alpha]_D^{26}$ +91.5° (MeOH), δ_H (D_2O) * 2.13 (3 H, s, 3-NAc), 2.96 and 3.10 [3 H, 2 s, 3-NCH_3(Ac)], 3.40 and 3.53 (3 H, 2 s, 1-OCH_3) and 4.33 (1 H, d, $J_{1,2}$ 8 Hz, 1-H).

Methyl 2,4-*Di*-O-*benzyl*-3-*deoxy*-3-N-*methylacetamido*-α- *and* -β-L-*arabinopyranoside* (21) *and* (22).—Methyl 3-deoxy-3-*N*-methylacetamido-α- and -β-L-arabinopyranoside (19) and (20) (6.8 g) were dissolved in dry tetrahydrofuran (200 ml). Hexane-washed sodium hydride (7.5 g) in dry tetrahydrofuran was added to the stirred solution and stirring was continued for 0.5 h at 25 °C. Benzyl bromide (38 ml) in dry tetrahydrofuran (200 ml) was added and the mixture was stirred at 25 °C for 70 h. The mixture was treated with acetic acid in light petroleum and then concentrated. The concentrate was taken up in chloroform, washed with water, and evaporated to dryness. Water was added and the mixture was evaporated *in vacuo*. The resulting gum was dried by azeotropic distillation of a benzene solution and then chromatographed on a silica-gel column (150 × 5 cm) using 1% v/v methanol–chloroform as the eluant to give the *methyl* α- and -β-L-*arabinopyranosides* (21) and (22) † (11.6 g, 94%) as a syrup (Found: C, 66.1; H, 7.0; N, 3.5. $C_{23}H_{29}NO_5 \cdot H_2O$ requires C, 66.2; H, 7.5; N, 3.35%), *m/e* 399 ($M^{+\cdot}$), 368, ($M - 31$), and 308 ($M - 91$), $[\alpha]_D^{26}$ +177.6° (MeOH), $\nu_{max.}$ ($CHCl_3$) 3 400, 1 730, 1 640, 1 060, and 698 cm^{-1}, δ_H ($CDCl_3$) * 1.97 and 2.09 (3 H, 2 s, 3-NAc), 2.91 and 3.00 [3 H, 2 s, 3-NCH_3(Ac)], 3.33 and 3.35 (3 H, 2 s, 1-OCH_3), 4.86 (1 H, d, $J_{1,2}$ 3 Hz, 1-H), and 7.27 (10 H, s, $OCH_2C_6H_5$).

1-O-*Acetyl*-2,4-*di*-O-*benzyl*-3-*deoxy*-3-N-*methylacetamido*-α- *and* -β-L-*arabinopyranose* (23) and (24).—Methyl 2,4-di-*O*-

* Mixture of rotamers at ambient temperature.

† Data recorded for material containing *ca.* 90% β-L-anomer (22).

benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-L-arabinopyranoside (21) (22) (9.9 g) was dissolved in glacial acetic acid (200 ml). 1M-Sulphuric acid (50 ml) was added and the mixture was heated at 85 °C for 13 h and then poured into ice–water. The solution was neutralized with sodium carbonate and extracted with chloroform. The chloroform extract was washed with water and evaporated to dryness, and the resulting gum was dried by azeotropic distillation from toluene. The gum (5.5 g) was dissolved in a mixture of sodium acetate (2 g) in acetic anhydride (50 ml) and the solution was heated at 85—90 °C for 2.2 h. The solution was concentrated to dryness, water was added, and the product was extracted into chloroform. The chloroform extract was evaporated to dryness and the residual gum was dried by azeotropic distillation from toluene and then chromatographed on a silica-gel column (105 × 3.5 cm) using 1% v/v methanol–chloroform as the eluant to give *the* α- and β-*pyranoses* (23) and (24) (4.0 g, 38%) as a syrup (Found: C, 65.2; H, 6.6; N, 2.9. $C_{24}H_{29}NO_6 \cdot H_2O$ requires C, 64.7; H, 7.0; N, 3.15%), *m/e* 428 [$(M + 1)^+$], 427 ($M^{+\cdot}$), 368 ($M - 59$), 336 ($M - 91$), $[\alpha]_D^{26}$ +122.6° (MeOH), δ_H ($CDCl_3$) * 1 97—2.12 (6 H, s, 1-OAc and 3-NAc), 2.87—3.00 [3 H, s, 3-NCH_3(Ac)], 5.64 (0.6 H, d, $J_{1ax,2ax}$ 8 Hz, 1*ax*-H), 6.57 (0.4 H, d, $J_{1eq,2ax}$ 3.5 Hz, 1*eq*-H), and 7.25 and 7.28 (10 H, s, $OCH_2C_6H_5$).

2,4-*Di*-O-*benzyl*-3-*deoxy*-3-N-*methylacetamido*-β-L-*arabinopyranosyl Chloride* (25).—1-*O*-Acetyl-2,4-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-L-arabinopyranose (23) and (24) (1.9 g) was dissolved in dioxan (100 ml) saturated with dry hydrogen chloride gas and acetyl chloride (50 ml) was added. The mixture was allowed to remain at 25 °C for 22.5 h and was then evaporated to dryness and azeotroped with toluene to give the glycosyl chloride (25) (1.79 g, 99%) as a labile syrup, δ_H ($CDCl_3$) * 1.98 and 2.04 (3 H, 2 s, 3-NAc), 2.90 and 3.00 [3 H, 2 s, 3-NCH_3(Ac)], 5.02 (1 H, dd, $J_{1eq,2ax}$ 3.5, $J_{2ax,3ax}$ 11 Hz, 2*ax*-H), and 6.42 (1 H, d, $J_{1eq,2ax}$ 3.5 Hz, 1-H). Owing to the unstable nature of the product it was used without further purification.

O-3-*Deoxy*-3-*methylamino*-β-L-*arabinopyranosyl*-(1 ⟶ 6)-*gentamine* C_{1a} (7).[12]—1,3,2′,6′-Tetrakis-*N*-benzyloxycarbonylgentamine C_{1a} (4) (1.9 g), 2,4-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-β-L-arabinopyranosyl chloride (25) (1.79 g), and silver toluene-*p*-sulphonate (1.6 g) were dissolved in dry dichloromethane (110 ml) and the mixture was stirred at 25 °C for 21.25 h. The solids were filtered off, washed with dichloromethane, and the combined filtrates were evaporated to dryness. The solid was chromatographed on a silica-gel column (102 × 3.5 cm) using 1% increasing to 30% v/v methanol–chloroform as the eluant to give *O*-2,4-*di*-O-*benzyl*-3-*deoxy*-3-N-*methylacetamido*-β-L-*arabinopyranosyl*-(1 ⟶ 6)-1,3,2′,6′-*tetrakis*-N-*benzyloxycarbonylgentamine* C_{1a} (8) (416 mg, 15%) as an amorphous solid (Found: C, 65.0; H, 6.5; N, 5.5. $C_{66}H_{75}N_5O_{16}$ requires: C, 66.4; H, 6.3; N, 5.9%), δ_H ($CDCl_3$) * 1.93br and 2.09br (3 H, 2 s, NAc), 2.79br and 2.97br [3 H, 2 s, NCH_3(Ac)] and 7.32br (30 H, s, $OCH_2C_6H_5$).

The protected pseudotrisaccharide (8) (835 mg) was dissolved in liquid ammonia at −79 °C and sodium (800 mg) was added in small portions. The mixture was stirred at −79 °C for 6 h and it was then quenched by dropwise addition of water and the ammonia was allowed to evaporate overnight. Water (50 ml) was added and the solution was heated under reflux for 5.5 h. The solution was cooled and neutralized with Amberlite IRC 50 (H^+) resin, and the resin was washed with water. Elution of the resin with 1.5M-ammonium hydroxide was followed by evaporation and chromatography of the resulting gum on a silica-gel column (132 × 1.5 cm) using a chloroform–methanol–3.5% v/v ammonium hydroxide (1 : 2 : 1 v/v) as the eluant. The product was rechromatographed twice on a silica-gel column (100 × 1 cm) using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide solution (1 : 1 : 1 v/v) as the eluant to give O-3-*deoxy*-3-*methylamino*-β-L-*arabinopyranosyl*-(1 ⟶ 6)-*gentamine* C_{1a} (7) [12] (22 mg, 7%) as an amorphous solid after passage over Amberlite IRA 401S (OH^-) resin followed by lyophilization [Found: $(M + 1)^+$, 436.2752. $C_{18}H_{38}N_5O_7$ requires M + 1, 436.2771], $[\alpha]_D^{26}$ +136.2° (H_2O) {lit.,[12] $[\alpha]_D^{20}$ +144° (H_2O)}, δ_H (D_2O) 2.39 (3 H, s, 3″-NCH_3), 3.78 (1 H, dd, $J_{1'',2''}$ 4, $J_{2'',3''}$ 11 Hz, 2″-H), 5.09 (1 H, d, $J_{1eq'',2ax''}$ 4 Hz, 1*eq*″-H), and 5.19 (1 H, d, $J_{1eq',2ax'}$ 3.5 Hz, 1 *eq*′-H).

Methyl 3-Acetamido-2,4-di-O-benzyl-3-deoxy-β-D-xylopyranoside (27).—Methyl 3-acetamido-3-deoxy-β-D-xylopyranoside (26) (50 g) was dissolved in dry dimethylformamide (1 l) and the solution was cooled to 0 °C. Benzyl bromide (500 g), barium oxide (370 g), and barium hydroxide octahydrate (170 g) were added and the mixture was stirred at 25 °C for 17 h. The mixture was diluted and the solids were filtered off. The filtrate was evaporated to dryness to give the 2,4-*di*-O-*benzyl derivative* (27) which crystallized from ethanol–methanol as needles (52.3 g, 56%), m.p. 187—188 °C (Found: C, 68.5; H, 7.25; N, 3.55. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.1; N, 3.6%), *m/e* 386 [$(M + 1)^+$], 354 ($M - 31$), and 294 ($M - 91$), $[\alpha]_D^{25}$ −38.6° ($CHCl_3$), $\nu_{max.}$ (Nujol) 3 300, 1 660, 1 570, 1 090, 745, and 696 cm^{-1}, δ_H ($CDCl_3$) 1.87 (3 H, s, 3-NAc), 3.42 (3 H, s, 1-OCH_3), 4.46 (1 H, d, $J_{1ax,2ax}$ 5 Hz, 1*ax*-H) 4.60 and 4.70 (4 H, 2 s, $OCH_2C_6H_5$), 5.88br (1 H, d, J 8.5 Hz, 3-N*H*Ac), and 7.29 (10 H, s, $OCH_2C_6H_5$).

3-*Acetamido*-1-O-*acetyl*-2,4-*di*-O-*benzyl*-3-*deoxy*-α- *and* -β-D-*xylopyranose* (28) *and* (29).—Methyl 3-acetamido-2,4-di-*O*-benzyl-3-deoxy-β-D-xylopyranoside (27) (45 g) was dissolved in glacial acetic acid (800 ml) and 1M-sulphuric acid (200 ml) was added and the mixture was heated at 100 °C for 2.5 h. Additional 1M-sulphuric acid (200 ml) was added and the mixture was heated for a further 3 h at 100 °C. The solution was extracted with chloroform (2 × 500 ml). The chloroform extracts were dried ($MgSO_4$) and evaporated to dryness. The resulting solid (32 g) was dissolved in a mixture of acetic anhydride (300 ml) and sodium acetate (15 g) and the solution was heated at 100 °C for 4 h. The solution was poured into ice–water (1 l) and the resulting precipitate of the *acetyl* α- and β-*pyranoses* (28) and (29) crystallized as needles from ethanol–tetrahydrofuran (25.5 g, 53%), m.p. 204—206 °C (Found: C, 66.5; H, 6.3; N, 3.3. $C_{23}H_{27}NO_6$ requires C, 66.8; H, 6.6; N, 3.4%), *m/e* 414 [$(M + 1)^+$], 354 ($M - 59$), and 322 ($M - 91$), $[\alpha]_D^{26}$ +6.0° ($CHCl_3$), $\nu_{max.}$ (Nujol) 3 300, 1 760, 1 650, 1 560, 1 235, 1 090, 740, and 695 cm^{-1}, δ_H ($CDCl_3$) 1.86 (3 H, s, 3-NAc), 2.03 (3 H, s, 1-OAc), 4.52 and 4.63 (4 H, 2 s, $OCH_2C_6H_5$), and 7.26 (10 H, s, $OCH_2C_6H_5$).

3-*Acetamido*-2,4-*di*-O-*benzyl*-3-*deoxy*-α-D-*xylopyranosyl Chloride* (30).—3-Acetamido-1-*O*-acetyl-2,4-di-*O*-benzyl-3-deoxy-α- and -β-D-xylopyranose (28) and (29) (8.25 g) was dissolved in a saturated solution of dry hydrogen chloride in dioxan (400 ml). Acetyl chloride (200 ml) was added and the mixture was allowed to remain at 25 °C for 4.5 h. The solution was evaporated to dryness to give the *chloride*

* Mixture of rotamers at ambient temperature.

(30) (7.5 g, 96%) which crystallized from acetone–hexane as needles, m.p. 130—132 °C (decomp.) (Found: C, 65.0; H, 6.0; Cl, 9.0; N, 3.6. $C_{21}H_{24}ClNO_4$ requires C, 64.7; H, 6.2; Cl, 9.1; N, 3.6), $[\alpha]_D^{26}$ +107.1° ($CHCl_3$), $\nu_{max.}$ (Nujol) 3 300, 1 660, 1 560, 1 095, 747, and 697 cm^{-1}, δ_H ($CDCl_3$) 1.89 (3 H, s, 3-NHAc), 4.54 (4 H, s, $OCH_2C_6H_5$), 6.05 (1 H, d, $J_{1eq,2ax}$ 3.5 Hz, 1*eq*-H), and 7.31 (10 H, s, $OCH_2C_6H_5$).

O-3-*Amino-3-deoxy-α-*D*-xylopyranosyl-*(1 ⟶ 6)*-gentamine* C$_{1a}$ (10), O-3-*Amino-3-deoxy-β-*D*-xylopyranosyl-*(1 ⟶ 6)*-gentamine* C$_{1a}$ (40), *and* O-3-*Amino-3-deoxy-β-*D*-xylopyranosyl-*(1 ⟶ 5)*-gentamine* C$_{1a}$ (44).—1,3,2′,6′-Tetrakis-*N*-benzyloxycarbonylgentamine C$_{1a}$ (4) (6.2 g) was dissolved in dry dichloromethane (500 ml). Silver toluene-*p*-sulphonate (5.6 g) and 3-acetamido-2,4-di-*O*-benzyl-3-deoxy-α-D-xylopyranosyl chloride (30) (6.2 g) were added and the mixture was stirred at 25 °C for 18 h. The solids were filtered off and washed with dichloromethane, and the filtrate was evaporated to dryness. The resulting crude gum (12.6 g) was chromatographed on a silica-gel column (110 × 5 cm) using 1% v/v ethanol–chloroform as the eluant to give the protected pseudo-trisaccharides (2.6 g) as an amorphous solid. A slurry of the latter in dry tetrahydrofuran (20 ml) was added to liquid ammonia (400 ml) at −79 °C and sodium (2.1 g) was added in small portions. The mixture was stirred at −79 °C for 1.5 h and the reaction was worked up as described for (7). The ammoniacal eluant was evaporated to dryness and the solid was chromatographed on a silica-gel column (160 × 2.5 cm) using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide solution (1 : 1 : 1 v/v) as the eluant to give O-3-*amino-3-deoxy-β-*D*-xylopyranosyl-*(1 ⟶ 6)*-gentamine* C$_{1a}$ (40) (65 mg, 2%) as an amorphous solid after passage over Amberlite IRA 401S (OH^-) resin followed by lyophilization [Found: $(M+1)^+$, 422.2593. $C_{17}H_{36}N_5O_7$ requires M + 1, 422.2614], $[\alpha]_D^{26}$ 37.4° (H_2O), ν_{max} (KCl) 3 300 and 1 040 cm^{-1}, δ_H (D_2O) *ca.* 4.67 (1 H, d, *J* obscured by HOD, 1*ax*″-H) and 5.20 (1 H, d, $J_{1eq',2ax'}$ 3.5 Hz, 1*eq*′-H), and O-3-*amino-3-deoxy-α-*D*-xylopyranosyl-*(1 ⟶ 6)*-gentamine* C$_{1a}$ (10) (98 mg, 3%) as an amorphous solid after passage over Amberlite IRA 401S (OH^-) resin followed by lyophilization [Found: $(M+1)^+$, 422.2596. $C_{17}H_{36}N_5O_7$ requires M + 1, 422.2614], $[\alpha]_D^{26}$ +121.2° (H_2O), δ_H (D_2O) 5.07 (1 H, d, $J_{1eq'',2ax''}$ 3.5 Hz, 1*eq*″-H) and 5.24 (1 H, d, $J_{1eq',2ax'}$ 3.5 Hz, 1*eq*′-H). The more polar fractions were combined and rechromatographed on a silica-gel column (160 × 1.5 cm) using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide solution (2 : 1 : 1 v/v) as the eluant to give O-3-*amino-3-deoxy-β-*D*-xylopyranosyl-*(1 ⟶ 5)*-gentamine* C$_{1a}$ (44) (30 mg, 1%) as an amorphous solid after the passage over Amberlite IRA 401S (OH^-) resin followed by lyophilization (Found: $M^{+\bullet}$, 421 2533. $C_{17}H_{35}N_5O_7$ requires M, 421.2533), $[\alpha]_D^{26}$ +38.8° (H_2O), δ_H (D_2O) 4.75 (1 H, d, $J_{1ax'',2ax''}$ 7.5 Hz, 1*ax*″-H) and 4.93 (1 H, d, $J_{1eq',2ax'}$ 3.5 Hz, 1*eq*′-H).

3-*Deoxy-*1,2:5,6-*di-*O*-isopropylidene-*3-N*-methylacetamido-α-*D*-glucofuranose* (46).—3-Acetamido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (45) [15–17] (40 g) was dissolved in dry dimethylformamide (500 ml). Hexane-washed sodium hydride (18 g) was added and the mixture was stirred at 25 °C for 0.5 h and then cooled to 0 °C. Methyl iodide (100 g) was added and the mixture was stirred at 0 °C for 2 h. A 20% v/v methanol–ether was added to destroy the excess of sodium hydride and the solids were filtered off and washed with chloroform. The combined filtrates were partitioned between water and chloroform and the aqueous layer was washed with chloroform (× 3). The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The resulting N-*methyl derivative* (46) crystallized from methanol as needles (32 g, 77%), m.p. 128—130 °C (Found: C, 56.8; H, 8.2; N, 4.5. $C_{15}H_{25}NO_6$ requires C, 57.1; H, 8.0; N, 4.4%), *m/e* 315 ($M^{+\bullet}$), 314 (M − 1), 300 (M − 15), and 214 (*a*), $[\alpha]_D^{26}$ +5.5° ($CHCl_3$), δ_H ($CDCl_3$) * 1.31, 1.33, 1.42, 1.51, and 1.55 [12 H, 5 s, $OC(CH_3)_2O$], 2.11 and 2.23 (3 H, s, 3-NAc), 2.88 and 3.09 [3 H, 2 s, 3-NCH_3(Ac)], 4.72 and 4.96 (1 H, d, $J_{1,2}$ 3.8, $J_{2,3}$ 0 Hz, 2-H), and 5.98 and 6.11 (1 H, d, $J_{1,2}$ 3.8 Hz, 1-H).

3-*Deoxy-*1,2-O*-isopropylidene-*3-N*-methylacetamido-α-*D*-glucofuranose* (47).—3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*N*-methylacetamido-α-D-glucofuranose (46) (30 g) was dissolved in 50% aqueous acetic acid (600 ml) and the solution was allowed to remain at 25 °C for 20 h. The solution was evaporated to dryness and co-distilled with water to remove the last traces of acetic acid. The resulting syrup was dried (25.9 g, 99%) and a portion was chromatographed on silica gel (300 g) using chloroform as the eluant to give the 1,2-O-*isopropylidene derivative* (47) as a syrup (Found: $M^{+\bullet}$, 275.1357. $C_{12}H_{21}NO_6$ requires M, 275.1369), *m/e* 276 (M^+ + 1), 275 ($M^{+\bullet}$), 274 (M − 1), 260 (M − 15), 214 (*a*), $[\alpha]_D^{26}$ +83.5° ($CHCl_3$), δ_H ($CDCl_3$) * 1.33 and 1.54 [6 H, 2 s, $OC(CH_3)_2O$], 2.20 and 2.26 (3 H, s, 3-NAc), 2.87 and 2.98 [3 H, 2 s, 3-NCH_3(Ac)], 4.84 (1 H, d, $J_{1,2}$ 3.8, $J_{2,3}$ 0 Hz, 2-H), and 5.97 (1 H, d, $J_{1,2}$ 3.8 Hz, 1-H).

3-*Deoxy-*1,2-O*-isopropylidene-*3-N*-methylacetamido-α-*D*-xylofuranose* (48).—3-Deoxy-1,2-*O*-isopropylidene-3-*N*-methylacetamido-α-D-glucofuranose (47) (41 g) was dissolved in water (300 ml) and a solution of sodium metaperiodate (50 g) in water (400 ml) was added. The solution was allowed to remain at 25 °C for 3 h and was then cooled to 0 °C. Methanol (3 l) was added with stirring and the slurry was stirred for 1.5 h. The solids were filtered off using a Celite bed and the filtrate and methanol washings were evaporated. Ethanol (800 ml) and water (200 ml) were added followed by sodium borohydride (20 g) and the mixture was stirred at 25 °C for 2 h. The solution was diluted with methanol (1 l), neutralized with Amberlite IR 120 (H^+) resin, filtered, and evaporated to dryness. The syrup was chromatographed on silica gel (1.2 kg) using 10% v/v methanol–ethyl acetate as the eluant to give the α-D-*xylofuranose* (48) (36.1 g, 99%) as a syrup [Found: $(M-1)^+$, 244.1173. $C_{11}H_{18}NO_5$ requires M − 1, 244.1185], *m/e* 246 [$(M+1)^+$], 245 ($M^{+\bullet}$), 244 (M − 1), 230 (M − 15), and 214 (*a*), $[\alpha]_D^{26}$ +74.0° ($CHCl_3$), δ_H ($CDCl_3$) * 1.33 and 1.55 [6 H, 2 s, −O−$C(CH_3)_2O$], 2.18 (3 H, s, 3-NAc), 2.87 and 2.98 [3 H, 2 s, 3-NCH_3(Ac)], 4.88 (1 H, d, $J_{1,2}$ 4, $J_{2,3}$ 0 Hz, 2-H), and 6.04 (1 H, d, $J_{1,2}$ 4 Hz, 1-H).

5-O-*Benzyl-*3-*deoxy-*1,2-O*-isopropylidene-*3-N*-methylacetamido-α-*D*-xylofuranose* (49).—3-Deoxy-1,2-*O*-isopropylidene-3-*N*-methylacetamido-α-D-xylofuranose (48) (34.1 g) was dissolved in dry dimethylformamide (600 ml), and barium oxide (260 g) and barium hydroxide octahydrate (120 g) were added. Benzyl bromide (300 ml) was added to the stirred solution at 0 °C and after 1 h the mixture was diluted with chloroform and the solids were filtered off. The combined filtrate and washings were evaporated to dryness and the resulting syrup was chromatographed on silica gel (1 kg) using initially chloroform–hexane (1 : 1 v/v) and then chloroform–hexane (3 : 1 v/v) as the eluant to give the 5-O-*benzyl derivative* (49) (21.5 g, 46%) as a syrup

* Mixture of rotamers at ambient temperature.

(Found: $M^{+\cdot}$, 335.1747. $C_{18}H_{25}NO_5$ requires *M*, 355.1733), *m/e* 335 ($M^{+\cdot}$), 334 (*M* − 1), 320 (*M* − 15), and 214 (*a*), $[\alpha]_D^{26}$ +26.7° ($CHCl_3$), δ_H ($CDCl_3$) * 1.32 and 1.53 [6 H, 2 s, $OC(CH_3)_2O$], 2.02 and 2.14 (3 H, 2 s, 3-NAc), 2.84 and 2.90 [3 H, 2 s, 3-NCH_3(Ac)], 4.76 (1 H, d, $J_{1,2}$ 3.8, $J_{2,3}$ 0 Hz, 2-H), 5.98 and 6.04 (1 H, d, $J_{1,2}$ 3.8 Hz, 1-H), and 7.34 (5 H, s, $OCH_2C_6H_5$).

Methyl 5-O-*Benzyl-3-deoxy-3-methylamino-α- and -β-D-xylofuranoside* (50) *and* (51).—5-*O*-Benzyl-3-deoxy-1,2-*O*-isopropylidene-3-*N*-methylacetamido-α-D-xylofuranose (49) (1.19 g) was dissolved in dioxan (25 ml) and 0.1M-hydrochloric acid (25 ml) was added. The solution was heated under reflux at 90 °C for 2 h and then evaporated to dryness. The syrup was co-evaporated with methanol (×2) and then dissolved in 1% hydrogen chloride in methanol (25 ml) and heated under reflux for 2 h. The solution was cooled, neutralized with Amberlite IRA 401S (OH^-) resin, filtered, and the combined methanol–water filtrate and washings were evaporated to dryness. The resulting syrup was chromatographed on silica gel (50 g) using 1% v/v methanol–chloroform as the eluant to give the *amino-α-furanoside* (50) (113 mg, 12%) as a syrup (Found: $M^{+\cdot}$, 267.1462. $C_{14}H_{21}NO_4$ requires *M*, 267.1470), *m/e* 267 ($M^{+\cdot}$), 236 (*b*), 176 (*e*), and 146 (*f*), $[\alpha]_D^{26}$ +107.5° ($CHCl_3$), δ_H ($CHCl_3$) 2.47 (3 H, s, 3-NCH_3), 3.17 (1 H, dd, $J_{2,3}$ = $J_{3,4}$ = 7.5 Hz, 3-H), 3.44 (3 H, s, 1-OCH_3), 3.63 (2 H, d, $J_{4,5}$ 4 Hz, 5-CH_2), 4.04 (1 H, dd, $J_{1,2}$ 4.5, $J_{2,3}$ 7.5 Hz, 2-H), 4.28 (1 H, dd, $J_{3,4}$ 7.5, $J_{4,5}$ 4 Hz, 4-H), 4.54 (2 H, s, $OCH_2C_6H_5$), 4.84 (1 H, d, $J_{1,2}$ 4.5 Hz, 1-H), and 7.32 (5 H, s, $OCH_2C_6H_5$), and the *β-anomer* (51) (128 mg, 14%) as a syrup (Found: $M^{+\cdot}$, 267.1461. $C_{14}H_{21}NO_4$ requires *M*, 267.1470), *m/e* 268 [$(M + 1)^+$], 267 ($M^{+\cdot}$), 236 (*b*), 176 (*e*), and 146 (*f*), $[\alpha]_D^{26}$ −37.6° ($CHCl_3$), δ_H ($CDCl_3$) 2.39 (3 H, s, 3-NCH_3), 3.04 (1 H, dd, $J_{2,3}$ 3.5, $J_{3,4}$ 6.5 Hz, 3-H), 3.32 (3 H, s, 1-OCH_3), 4.08 (1 H, dd, $J_{1,2}$ 1.5, $J_{2,3}$ 3.5 Hz, 2-H), 4.57 (2 H, s, $OCH_2C_6H_5$), 4.76 (1 H, d, $J_{1,2}$ 1.5 Hz, 1-H), and 7.32 (5 H, s, $OCH_2C_6H_5$).

Methyl 5-O-*Benzyl-3-deoxy-3*-N-*methylacetamido-α- and -β-D-xylofuranoside* (52) *and* (53).—(*i*) 5-*O*-Benzyl-3-deoxy-1,2-*O*-isopropylidene-3-*N*-methylacetamido-α-D-xylofuranose (49) (25 g) was dissolved in dioxan (300 ml) and 0.1M-hydrochloric acid (300 ml) was added. The solution was heated under reflux at 90 °C for 3 h and then evaporated to dryness. The syrup was co-evaporated with methanol (×2) and then dissolved in 1% hydrogen chloride–methanol (100 ml) and heated under reflux for 3 h. The solution was cooled, neutralized with Amberlite IRA 401S (OH^-) resin, and filtered, and the combined methanol–water filtrate and washings were evaporated to dryness and dried *in vacuo*. The syrup was dissolved in methanol (300 ml) and acetic anhydride (100 ml) and allowed to remain at 25 °C for 1 h. The solution was evaporated to dryness and azeotroped with toluene, and the resulting syrup was chromatographed on silica gel (1 kg) using 1% v/v methanol–chloroform as the eluant to give a partial separation affording the *α-furanoside* (52) as a syrup (Found: C, 62.6; H, 7.5; N, 4.4%; M^+, 309.1553. $C_{16}H_{23}NO_5$ requires C, 62.1, H, 7.5; N, 4.5%; *M*, 309.1576), *m/e* 309 (M^+), 278 (*c*), 218 (*e*), and 188 (*g*), $[\alpha]_D^{26}$ +192.5° ($CHCl_3$), δ_H ($CDCl_3$) * 2.06 and 2.12 (3 H, 2 s, 3-NAc), 2.95 and 3.04 [3 H, 2 s, 3-NCH_3(OAc)], 3.50 (3 H, s, 1-OCH_3), 4.95 (1 H, d, $J_{1,2}$ 3.8 Hz, 1-H), and 7.34 (5 H, s, $OCH_2C_6H_5$), and the *β-anomer* (53) † as a syrup (Found: M^+, 309.1566. $C_{16}H_{23}NO_5$ requires *M*, 309.1576), *m/e* 309 ($M^{+\cdot}$), 278 (*c*), 218 (*e*), and 188 (*g*), $[\alpha]_D^{26}$ +21.7° ($CHCl_3$), δ_H ($CDCl_3$) * 2.03 and 2.11 (3 H, s, 3-NAc), 2.93 and 3.01 [3 H, s, 3-NCH_3(Ac)], 3.49 (3 H, s, 1-OCH_3), 4.56 (2 H, s, $OCH_2C_6H_5$), 4.88 (1 H, d, $J_{1,2}$ 3.8 Hz, 1-H), and 7.35 (5 H, s, $OCH_2C_6H_5$). All fractions containing the above products were combined to afford (52) and (53) as a syrup (23 g, 50%) containing a total of *ca.* 15% of the pyranosides (31) and (32) (as determined from the ^{1}H n.m.r. spectrum).

(*ii*) Methyl 5-*O*-benzyl-3-deoxy-3-methylamino-α-D-xylofuranoside (50) (39 mg) was dissolved in dry methanol (2 ml). Acetic anhydride (1 ml) was added and the mixture was allowed to remain at 25 °C for 1 h. The solution was evaporated to dryness and azeotroped with toluene to give (52) (45 mg, 100%) as a syrup. The product was identical (^{1}H n.m.r., $[\alpha]_D$, t.l.c.) with the sample prepared in (*i*).

(*iii*) Methyl 5-*O*-benzyl-3-deoxy-3-methylamino-β-D-xylofuranoside (51) (47 mg) was acetylated as described above to give the β-furanoside (53) (54 mg, 100%) as syrup. The pure β-furanoside (53) exhibited $[\alpha]_D^{26}$ +26.2° ($CHCl_3$) and the ^{1}H n.m.r. spectrum revealed the signals reported in (*ii*), but showed no peaks due to the pyranoside. The product was identical (t.l.c.) to the product prepared in (*ii*).

Methyl 2,5-Di-O-*benzyl-3-deoxy-3*-N-*methylacetamido-α- and -β-D-xylofuranoside* (54) *and* (55).—Methyl 5-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-D-xylofuranoside (52) and (53) (11 g) ‡ were dissolved in dry dimethylformamide (200 ml). Benzyl bromide (100 ml), barium oxide (74 g), and barium hydroxide octahydrate (34 g) were added to the stirred solution at 0 °C and the mixture was allowed to remain at 25 °C for 17 h. The reaction mixture was diluted with chloroform and filtered, and the combined filtrate and washings were evaporated to dryness. The resulting syrup was chromatographed on silica gel (400 g) using initially hexane and then chloroform–hexane (1 : 1 v/v) as the eluant, to give the *di-O-benzyl-α-furanoside* (54) as a syrup (Found: $M^{+\cdot}$, 399.2058. $C_{23}H_{29}NO_5$ requires *M*, 399.2046), *m/e* 399 ($M^{+\cdot}$), 368 (*d*) 278 (*h*), and 218 (*e*), $[\alpha]_D^{26}$ +7.0° ($CHCl_3$), δ_H ($CDCl_3$) * 2.00 and 2.14 (3 H, 2 s, 3-NAc), 2.86 and 2.92 [3 H, 2 s, 3-NCH_3(Ac)], 3.43 (3 H, s, 1-OCH_3), 4.93 (1 H, d, $J_{1,2}$ 3.3 Hz, 1-H), and 7.30 (10 H, s, $OCH_2C_6H_5$), and the *β-anomer* (55) § as a syrup (Found: $M^{+\cdot}$, 399.2040. $C_{23}H_{29}NO_5$ requires *M* 399.2046), *m/e* 399 ($M^{+\cdot}$), 368 (*d*), 278 (*i*), and 218 (*e*), $[\alpha]_D^{26}$ +81.0° ($CHCl_3$), δ_H ($CDCl_3$) * 1.94 and 2.04 (3 H, 2 s, 3-NAc), 2.77 and 2.79 [3 H, 2 s, 3-NCH_3(Ac)], 3.41 (3 H, s, 1-OCH_3), and 7.30 and 7.32 (10 H, 2 s, $OCH_2C_6H_5$). All fractions containing the above products were combined to afford (54) and (55) as a syrup (11.4 g, 80%) containing a total of *ca.* 15% of the corresponding pyranosides (33) and (34) (^{1}H n.m.r.).

1-O-*Acetyl-2,5-di*-O-*benzyl-3-deoxy-3*-N-*methylacetamido-α- and -β-D-xylofuranose* (56) *and* (57) *and* 1-O-*Acetyl-2,4-di*-O-*benzyl-3-deoxy-3*-N-*methylacetamido-α- and -β-D-xylopyranose* (36) *and* (37).—Methyl 2,5-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-D-xylofuranoside (54) and (55) (9.5 g) containing 15% of the corresponding pyranosides (33) and (34) were dissolved in glacial acetic acid (150 ml) and 1M-hydrochloric acid (200 ml) and the solution was

* Mixture of rotamers at ambient temperature.

† The ^{1}H n.m.r. spectrum revealed signals at δ_H 2.12 due to the 3-NAc group and at δ_H 3.06 and 3.12 due to the 3-NCH_3 (Ac) group of the pyranosides (31) and (32) which was present to the extent of *ca.* 25—30% in the sample analysed.

‡ Containing *ca.* 15% of the corresponding pyranosides (31) and (32).

§ The ^{1}H n.m.r. spectrum of (55) indicated the presence of some of the pyranoside (34).

heated at 85 °C for 2 h. The solution was cooled, extracted with chloroform, and the chloroform extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness. The resulting syrup was dissolved in acetic anhydride (100 ml) and anhydrous sodium acetate (9 g) was added and the mixture was heated at 83 °C for 1 h. The mixture was cooled, poured into ice–water and extracted with chloroform. The chloroform extracts were washed with water, dried (Na_2SO_4), and evaporated. The products were azeotroped with toluene and then chromatographed on silica gel (300 g) using 5% v/v acetone–hexane as the eluant to give the 1-O-*acetyl*-α- and -β-*pyranoses* (36) and (37) (2.87 g, 28%) as a syrup (Found: $M^{+\cdot}$, 427.1987. $C_{24}H_{29}NO_6$ requires *M*, 427.1995), *m/e* 427 ($M^{+\cdot}$), 368 (*d*), and 336 (*j*), $[\alpha]_D^{26}$ +21.6° ($CHCl_3$), δ_H ($CDCl_3$) * 1.90, 1.98, 2.06, 2.08, 2.14, and 2.19 (6 H, 6 s, 3-NAc and 1-OAc), 2.53 and 2.66 [3 H, 2 s, 3-NCH_3(Ac)], 5.65 (0.7 H, d, $J_{1ax,2ax}$ 7.5 Hz, 1*ax*-H), 6.40 (0.3 H, d, $J_{1eq,2ax}$ 3.7 Hz, 1*eq*-H), and 7.32 (10 H, s, $-OCH_2C_6H_5$) and the 1-O-*acetyl*-α- and -β-*furanoses* (56) and (57) (1.48 g, 15%) as a syrup (Found: $M^{+\cdot}$ 427.1994. $C_{24}H_{29}NO_6$ requires *M*, 427.1995), *m/e* 427 ($M^{+\cdot}$) 368 (*d*), and 306 (*i*), $[\alpha]_D^{26}$ +12.3° ($CHCl_3$), δ_H ($CDCl_3$) * 2.01, 2.03, 2.06, 2.08, and 2.10 (6 H, s, 3-NAc and 1-OAc), 2.86 and 2.90 [3 H, s, 3-NCH_3(Ac)], 6.20 (0.7 H, d, $J_{1,2}$ 3 Hz, 1*ax*-H), 6.43 (0.3 H, d, $J_{1,2}$ 4 Hz, 1*eq*-H), and 7.28 and 7.34 (10 H, 2 s, $OCH_2C_6H_5$), and 1,4-*di*-O-*acetyl*-2,5-*di*-O-*benzyl*-3-*deoxy*-3-N-*methylacetamido*-D-threo-*pent*-1-*enose* (60) (269 mg, 2%) as a syrup, *m/e* 470 ($M^+ + 1$), 469 ($M^{+\cdot}$), 410 ($M - 59$), and 378 ($M - 91$), $[\alpha]_D^{26}$ +16.5° ($CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 1 730, 1 640, 1 220, 1 080, 1 020, and 693 cm^{-1}, δ_H ($CDCl_3$) * 2.01br (9 H, s, OAc and NAc), 2.88br [3 H, s, 3-NCH_3(Ac)], 4.51 and 4.59 (4 H, 2 s, $OCH_2C_6H_5$), and 7.33 (10 H, s, $OCH_2C_6H_5$).

1-O-*Acetyl*-2,4-*di*-O-*benzyl*-3-*deoxy*-3-N-*methylacetamido*-α- *and* -β-D-*xylopyranose* (36) *and* (37).—Methyl 3-acetamido-2,4-di-*O*-benzyl-3-deoxy-α- and -β-D-xylopyranoside (35) and (27) (413 mg) were dissolved in dry dimethylformamide (5 ml). Hexane-washed sodium hydride (150 mg) and methyl iodide (0.5 ml) were added and the mixture was stirred at 25 °C for 0.5 h. The reaction mixture was diluted with chloroform and filtered, and the filtrate was evaporated to afford methyl 2,4-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-D-xylopyranoside (33) and (34) (360 mg, 90%) as a syrup, *m/e* 399 ($M^{+\cdot}$), 368 ($M - 31$), and 308 ($M - 91$). The syrup was dissolved in glacial acetic acid (10 ml) and 2M-hydrochloric acid (10 ml), and the solution was heated at 90 °C for 4 h. The solution was partitioned with chloroform–water and the chloroform layer was dried (Na_2SO_4) and evaporated to dryness. The resulting syrup was dissolved in acetic anhydride (5 ml) containing anhydrous sodium acetate (300 mg) and the mixture was heated at 90 °C for 1 h. The solution was cooled, poured into ice–water, and extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and evaporated to afford the 1-*O*-acetyl-α- and -β-D-xylopyranoses (36) and (37) (244 mg, 63%) as a syrup, identical (t.l.c. and mass and ^1H n.m.r. spectra) with the sample prepared above.

2,4-*Di*-O-*benzyl*-3-*deoxy*-3-N-*methylacetamido*-α-D-*xylopyranosyl Chloride* (38).—1-*O*-Acetyl-2,4-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-D-xylopyranose (36) and (37) (2.8 g) was dissolved in a saturated solution of dry hydrogen chloride gas in dry dioxan (150 ml). Acetyl chloride (75 ml) was added and the solution was allowed to remain at 25 °C for 3.5 h. The solution was evaporated to dryness and azeotroped with toluene affording the chloride (38) (2.6 g, 98%) as a labile syrup which could not be induced to crystallize, $[\alpha]_D^{26}$ +54.7° ($CHCl_3$), δ_H ($CDCl_3$) * 1.90—2.10 (3 H, s, 3-NAc), 2.50—2.60 [3 H, s, 3-NCH_3(Ac)], 6.02 and 6.20 (1 H, 2 d, $J_{1eq,2ax}$ 3.5 Hz, 1*eq*-H), and 7.27 and 7.37 (10 H, 2 s, $OCH_2C_6H_5$). The chloride (38) was used without further purification.

O-3-*Deoxy*-3-*methylamino*-α-D-*xylopyranosyl*-(1 ⟶ 6)-*gentamine* C_1 (12) *and* O-3-*deoxy*-3-*methylamino*-β-D-*xylopyranosyl*-(1 ⟶ 6)-*gentamine* C_1 (42).—1,3,2′6′-Tetrakis-*N*-benzyloxycarbonylgentamine C_1 (3) (5.6 g) was dissolved in dry dichloromethane (200 ml) and dry silver toluene-*p*-sulphonate (2.1 g) was added. 2,4-Di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α-D-xylopyranosyl chloride (38) (2.5 g) dissolved in dry dichloromethane (100 ml) was added and the mixture was stirred at 25 °C for 90 h. The solids were filtered off and washed with dichloromethane and the combined filtrates were evaporated to dryness. The products were chromatographed on silica gel (600 g) using 1% v/v methanol–chloroform as the eluant to give *O*-2,4-*di*-O-*benzyl*-3-*deoxy*-3-*methylacetamido*-α- and -β-D-*xylopyranosyl*-(1 ⟶ 6)-1,3,2′,6′-*tetrakis*-N-*benzyloxycarbonylgentamine* C_1 (11) and (41) (4.9 g, 60%) as an amorphous solid (Found: C, 66.4; H, 6.5; N, 5.2. $C_{68}H_{79}N_5O_{17}$ requires C, 66.8; H, 6.5; N, 5.7%), δ_H ($CDCl_3$) * 1.08br and 1.21br (3 H, 2 m, 7′-CH_3), 1.90—2.15br (3 H, s, 3″-NAc), 2.53br, 2.68br, and 2.78br (6 H, 3 s, 6′-NCH_3 and 3″-NCH_3), 4.42br and 4.50br (4 H, 2 s, $OCH_2C_6H_5$), 5.12br (8 H, s, $CO_2CH_2C_6H_5$), and 7.37br (30 H, s, $OCH_2C_6H_5$).

The protected pseudotrisaccharides (11) (41) (3.5 g) were dissolved in dry tetrahydrofuran (30 ml) and the solution was added to liquid ammonia (600 ml) at −79 °C. Sodium metal was added in small portions until the blue colour persisted and the mixture was stirred at −79 °C for 0.5 h. The excess of sodium was destroyed by dropwise addition of methanol and the ammonia was allowed to distil off at 25 °C for 17 h. 1M-Sodium hydroxide (150 ml) was added and the mixture was heated under reflux for 7 h. The solution was cooled and neutralized with Amberlite IRC 50 (H^+) resin, and the resin was washed with water. The resin was eluted with 2M-ammonium hydroxide and the basic eluate was evaporated to dryness. The residue was chromatographed on silica gel (200 g) using chloroform–methanol–3.5% ammonium hydroxide (1 : 2 : 1 v/v) as the eluant and the major cuts were each rechromatographed (× 2) on silica gel (30—50 g) using in all instances the lower phase of a chloroform–methanol–concentrated ammonium hydroxide solution (2 : 1 : 1 v/v) as the eluant to give *O*-3-*deoxy*-3-*methylamino*-β-D-*xylopyranosyl*-(1 ⟶ 6)-*gentamine* C_1 (42) (59 mg, 5%) as an amorphous solid after passage over Amberlite IRA 401S (OH^-) resin followed by lyophilization [Found: $(M + 1)^+$, 464.3049. $C_{20}H_{42}N_5O_7$ requires $M + 1$, 464.3083], $[\alpha]_D^{26}$ +30.0° (H_2O), δ_H (D_2O) 1.06 (3 H, d, $J_{6',7'}$ 7 Hz, 7′-CH_3), 2.35 (3 H, s, 6′-NCH_3), 2.45 (3 H, s, 3″-NCH_3), 4.60 (1 H, d, $J_{1ax'',2ax''}$ *ca.* 8 Hz, 1*ax*″-H), and 5.13 (1 H, d, $J_{1eq',2ax'}$ 3.5 Hz, 1*eq*′-H), and *O*-3-*deoxy*-3-*methylamino*-α-D-*xylopyranosyl*-(1 ⟶ 6)-*gentamine* C_1 (12) (78 mg, 6%) as an amorphous solid after passage over Amberlite IRA 401S (OH^-) resin followed by lyophilization [Found: $(M + 1)^+$, 464.3031. $C_{20}H_{42}N_5O_7$ requires $M + 1$, 464.3084], $[\alpha]_D^{26}$ +103.2° (H_2O), δ_H (D_2O) 1.06 (3 H, d, $J_{6',7'}$ 7.5 Hz, 7′-CH_3), 2.35 (3 H, s, 6′-NCH_3), 2.45 (3 H, s, 3″-NCH_3), 5.03 (1 H, d, $J_{1eq'',2ax''}$ 3.5 Hz, 1*eq*″-H), and 5.15 (1 H, d, $J_{1eq',2ax'}$ 3.5 Hz, 1*eq*′-H).

* Mixture of rotamers at ambient temperature.

2,5-Di-O-benzyl-3-deoxy-3-N-methylacetamido-α- and -β-D-xylofuranosyl Chloride (58) *and* (59).—1-*O*-Acetyl-2,5-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-D-xylofuranose (56) and (57) (1.17 g) was dissolved in a saturated solution of dry hydrogen chloride gas in dry dioxan (75 ml). Acetyl chloride (40 ml) was added and the solution was allowed to remain at 25 °C for 5.5 h. The solution was evaporated to dryness and azeotroped with toluene affording the α- and β-D-furanosyl chlorides (58) and (59) (1.1 g, 99%) as a labile syrup which could not be induced to crystallize, $[\alpha]_D^{26}$ +99.7° ($CHCl_3$), δ_H ($CDCl_3$) * 2.00—2.08 (3 H, s, 3-NAc), 2.83—2.89 [3 H, s, 3-NCH_3(Ac)], 6.42 (1 H, d, $J_{1,2}$ 4 Hz, 1-H), and 7.38 (10 H, s, $OCH_2C_6H_5$). The chlorides (58) and (59) were used without further purification.

O-3-*Deoxy*-3-*methylamino*-α-D-*xylofuranosyl*-(1 ⟶ 5)-*gentamine* C_1 (64) *and* O-3-*Deoxy*-3-*methylamino*-α-D-*xylofuranosyl*-(1 ⟶ 6)-*gentamine* C_1 (62).—1,3,2′,6′-Tetrakis-*N*-benzyloxycarbonylgentamine C_1 (3) (2.7 g) was dissolved in dry dichloromethane (150 ml) and dry silver toluene-*p*-sulphonate (0.84 g) was added. 2,5-Di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α- and -β-D-xylofuranosyl chloride (58) and (59) (1.1 g) dissolved in dry dichloromethane (75 ml) was added and the mixture was stirred at 25 °C for 115 h. The solids were filtered off and washed with dichloromethane and the combined filtrates were evaporated to dryness. The products were chromatographed on silica gel (250 g) using 1% v/v methanol–chloroform as the eluant to give *O-2,5-di-*O*-benzyl-3-deoxy-3-*N*-methylacetamido-α-D-xylofuranosyl-*(1 ⟶ 6)- and (1 ⟶ 5)-1,3,2′,6′-*tetrakis*-N-*benzyloxycarbonylgentamine* C_1 (61) and (63) (1.82 g, 47%) as an amorphous solid (Found: C, 65.7; H, 6.30, N, 5.5. $C_{68}H_{79}N_5O_{17}$ requires C, 66.8; H, 6.5; N, 5.7%), δ_H ($CDCl_3$) * 1.10—1.30br (3 H, s, 7′-CH_3), 1.98br and 2.08br (3 H, 2 s, 3″-NAc), 2.66—2.82br (6 H, s, 6′-NCH_3 and 3″-NCH_3), 4.51br and 4.60br (4 H, 2 s, $OCH_2C_6H_5$), 5.09br (8 H, s, $CO_2CH_2C_6H_5$), and 7.35br (30 H, s, $OCH_2C_6H_5$).

The protected pseudotrisaccharides (61) and (63) (1.67 g) were dissolved in dry tetrahydrofuran (15 ml) and the solution was added to liquid ammonia (250 ml) at −79 °C. Sodium metal was added in small portions until the blue colour persisted and the mixture was stirred at −79 °C for 0.5 h. The excess of sodium was destroyed by dropwise addition of methanol and the ammonia was allowed to distil off at 25 °C for 17 h. 1M-Sodium hydroxide (75 ml) was added and the mixture was heated under reflux for 6 h. The reaction was worked up as described for (42). The residue was chromatographed on silica gel (150 g) using chloroform–methanol–3.5% ammonium hydroxide solution (1 : 2 : 1 v/v) as the eluant and the overlap fractions were rechromatographed on silica gel (20 g) using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide solution (2 : 1 : 1 v/v) as the eluant to give two major fractions. The latter were rechromatographed (×3) on silica gel columns (40 g, 50 g, and 60 g) using in each instance the lower phase of a chloroform–methanol–concentrated ammonium hydroxide solution (2 : 1 : 1 v/v) as the eluant to give *O-3-deoxy-3-methylamino-α-D-xylofuranosyl-*(1 ⟶ 5)-*gentamine* C_1 (64) (63 mg, 10%) as an amorphous solid after passage over Amberlite IRA 401S (OH^-) resin followed by lyophilization [Found: $(M + 1)^+$, 464.3028. $C_{20}H_{42}N_5O_7$ requires $M + 1$, 464.3083], $[\alpha]_D^{26}$ +85.6° (H_2O), δ_H (D_2O) 1.05 (3 H, d, $J_{6',7'}$ 7 Hz, 7′-CH_3), 2.35 (3 H, s, 6′-NCH_3), 2.42 (3 H, s, 3″-NCH_3), 4.17 (1 H, dd, $J_{1'',2''}$ 4.5, $J_{2'',3''}$ 7.5 Hz, 2″-H), 5.19 (1 H, d, $J_{1',2'}$ 3.5 Hz, 1′-H), and 5.22 (1 H, d, $J_{1'',2''}$ 4.5 Hz, 1″-H), and *O-3-deoxy-3-methylamino-α-D-xylofuranosyl-*(1 ⟶ 6)-*gentamine* C_1 (62) (66 mg, 10%) as an amorphous solid after passage over Amberlite IRA 401S (OH^-) resin followed by lyophilization [Found: $(M + 1)^+$, 464.3048. $C_{20}H_{42}N_5O_7$ requires $M + 1$, 464.3083], $[\alpha]^{26}$ +101.3° (H_2O), $[\theta]_{278}$ +400 (TACu), δ_H (D_2O) 1.08 (3 H, d, $J_{6',7'}$ 7 Hz, 7′-CH_3), 2.38 (3 H, s, 6′-NCH_3), 2.43 (3 H, s, 3″-NCH_3), 4.18 (1 H, dd, $J_{1'',2''}$ 4.5, $J_{2'',3''}$ 8 Hz, 2″-H), 5.18 (1 H, d, $J_{1',2'}$ 3.5 Hz, 1′-H), and 5.20 (1 H, d, $J_{1'',2''}$ 4.5 Hz, 1″-H).

O-β-D-*Xylofuranosyl*-(1 ⟶ 6)-*gentamine* C_1 (70).—1,3,2′,6′-Tetrakis-*N*-benzyloxycarbonylgentamine C_1 (3) (1 g) was dissolved in dry toluene (75 ml) and dry calcium sulphate (baked out on a hot-plate) (5.2 g), mercury(II) cyanide (1.6 g), and 2,3,5-tri-*O*-acetyl-α- and -β-D-xylofuranosyl bromide (65) and (66) [18] (1.1 g) were added. The mixture was heated at 100 °C under nitrogen for 24 h and the temperature was then lowered to 60 °C and additional bromo-sugar (65) and (66) (396 mg) was added. After a further 24 h at 60 °C additional bromo-sugar (65) and (66) (993 mg) was added and heating was continued at 60 °C for 24 h. The mixture was cooled and filtered, and the residue was washed with ethyl acetate. The combined filtrates were washed with 20% aqueous potassium bromide and water, dried (Na_2SO_4), filtered, and evaporated. The residue was triturated with ether–hexane (3 : 1 v/v) (100 ml) and the solid was then chromatographed on silica gel plates using ether–benzene–methanol (49.5 : 49.5 : 1 v/v) as the eluant (developed 3 times) to give O-2,3,5-*tri*-O-*acetyl*-β-D-*xylofuranosyl*-(1 ⟶ 6)-1,3,2′,6′-*tetrakis*-N-*benzyloxycarbonylgentamine* C_1 (69) (159 mg, 12%) as an amorphous solid (Found: C, 61.3; H, 6.2; N, 5.2. $C_{57}H_{68}N_4O_{19}$ requires C, 61.50; H, 6.2; N, 5.0%), δ_H [$CDCl_3$–CD_3OD (3 : 1)] 1.14 (3 H, d, $J_{6',7'}$ 7 Hz, 7′-CH_3), 1.97br, 2.02br, and 2.05br (9 H, 3 s, OAc), 2.66br (3 H, s, 6′-NCH_3), and 7.37 (20 H, s, $CH_2C_6H_5$).

The product (69) (119 mg) was dissolved in methanol (100 ml) and concentrated ammonium hydroxide (20 ml), and the solution was stirred at 25 °C for 18 h. The solution was evaporated to dryness and the residue was dissolved in liquid ammonia (200 ml) at −78 °C, sodium (400 mg) was added, and the mixture was stirred for 2 h. Water (10 ml) was added dropwise and the ammonia was allowed to evaporate. The residue was dissolved in water and neutralized with Bio Rex 70 (H^+) resin (30 ml). The resin was washed with water and then eluted with 1.5M-ammonium hydroxide. The eluate was evaporated to dryness and the residue was chromatographed on silica gel (5 g) using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide solution (1 : 1 : 1 v/v) as the eluant to give *O-β-D-xylofuranosyl-*(1 ⟶ 6)-*gentamine* C_1 (70) (7 mg, 10%) as an amorphous solid (Found: $M^{+\bullet}$, 450.2673. $C_{19}H_{33}N_4O_8$ requires M, 450.2688), δ_H (D_2O) 1.13 (3 H, d, $J_{6',7'}$ 7 Hz, 7′-CH_3), 2.47 (3 H, s, 6′-NCH_3), 5.18 (1 H, d, $J_{1eq',2ax'}$ 4 Hz, 1*eq*′-H), and 5.32 (1 H, s, 1″-H).

O-β-D-*Ribofuranosyl*-(1 ⟶ 6)-*gentamine* C_1 (72) *and* O-β-D-*Ribofuranosyl*-(1 ⟶ 5)-*gentamine* C_1 (74).—1,3,2′,6′-Tetrakis-*N*-benzyloxycarbonylgentamine C_1 (3) (1 g) was dissolved in dry toluene (75 ml) and dry dioxan (75 ml) and dry calcium sulphate (ground and baked out on a hot-plate) (5.2 g), mercury(II) cyanide (1.6 g), and 2,3,5-tri-*O*-benzoyl-α- and -β-D-ribofuranosyl bromide (67) and (68) [19] (1.38 g) were added. The mixture was heated at 95 °C under nitrogen for 4 days. The mixture was cooled and filtered, and

* Mixture of rotamers at ambient temperature.

the residue was washed with ethyl acetate. The combined filtrates were washed with 20% aqueous potassium bromide and water, dried (Na_2SO_4), filtered, and evaporated. The residue was triturated twice with diethyl ether (50 ml) to give *O-2,3,5-tri-O-benzoyl-β-D-ribofuranosyl-(1 ⟶ 6)-1,3,2′,6′-tetrakis-N-benzyloxycarbonylgentamine C_1* (71) (999 mg). Additional (71) (120 mg) (1.1 g, 74%) was obtained by chromatography of the ether-soluble fractions on silica-gel plates using ether–benzene–methanol (49.75 : 49.75 : 0.5 v/v) as the eluant. The β-anomer (71) crystallized from acetone–ether (Found: C, 66.3; H, 5.7; N, 4.60. $C_{72}H_{75}N_4O_{19}$ requires C, 66.5; H, 5.8; N, 4.3%), δ_H [$CDCl_3$–CD_3OD (3 : 1)] 1.15 (3 H, d, $J_{6',7'}$ 6 Hz, 7′-CH_3), 2.67br (3 H, s, 6′-NCH_3), 7.35 (29 H, m, $CH_2C_6H_5$ and Bz), and 8.00 (6 H, m, Bz).

A second band from the t.l.c. afforded *O-2,3,5-tri-O-benzoyl-β-D-ribofuranosyl-(1 ⟶ 5)-1,3,2′,6′-tetrakis-N-benzyloxycarbonylgentamine C_1* (73) (131 mg, 11%) which crystallized from acetone–ether (Found: C, 66.1; H, 5.6; N, 4.5. $C_{72}H_{75}N_4O_{19}$ requires C, 66.5; H, 5.8; N, 4.3%), δ_H [$CDCl_3$–CD_3OD (3 : 1)] 1.10 (3 H, d, $J_{6',7'}$ 6 Hz, 7′-CH_3), 2.67br (3 H, s, 6′-NCH_3), 7.35 (29 H, m, $CH_2C_6H_5$ and Bz), and 8.00 (6 H, m, Bz).

The β-anomer (71) (900 mg) was dissolved in warm methanol (100 ml), cooled to 25 °C and the solution was treated with concentrated ammonium hydroxide (20 ml) and stirred at 25 °C for 18 h. The solution was evaporated to dryness and the residue was dissolved in liquid ammonia (200 ml) at −78 °C. Sodium (400 mg) was added and the mixture was stirred for 2 h. The reaction was worked up as described for (70). The eluate was evaporated to dryness and the residue was chromatographed on silica gel (13 g) using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide solution (2 : 1 : 1 v/v) as the eluant to give *O-β-D-ribofuranosyl-(1 ⟶ 6)-gentamine C_1* (72) (171 mg, 55%) as an amorphous solid, $[\theta]_{305}$ −4 560 (TACu), $[\theta]_{305}$ −4 580 (Cupra A) (Found: *m/e*, 422.2540. $C_{19}H_{36}N_4O_7$ requires *M* − H_2O, 432.2583), δ_H (D_2O) 1.23 (3 H, d, $J_{6',7'}$ 7 Hz, 7′-CH_3), 2.52 (3 H, s, 6′-NCH_3), 5.25 (1 H, d, $J_{1eq',2ax'}$ 4 Hz, 1*eq*′-H), and 5.37 (1 H, s, 1″-H).

The β-anomer (73) (120 mg) was deprotected as described above and chromatographed on silica gel (5 g) using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide solution (2 : 1 : 1 v/v) as the eluant to give *O*-β-D-ribofuranosyl-(1 ⟶ 5)-gentamine C_1 (74) (9 mg, 22%) as an amorphous solid, δ_H (D_2O) 1.18 (3 H, d, $J_{6',7'}$ 6 Hz, 7′-CH_3), 2.48 (3 H, s, 6′-NCH_3), 5.39 (1 H, d, $J_{1eq',2ax'}$ 4 Hz, 1*eq*′-H), and 5.40 (1 H, s, 1″-H).

O-α-D-Arabinopyranosyl-(1 ⟶ 6)-gentamine C_1 (79).—1,3,2′,6′-Tetrakis-*N*-benzyloxycarbonylgentamine C_1 (3) (1.5 g) was dissolved in dry toluene (72 ml) and dry dioxan (51 ml), and Drierite (ground and baked out on a hot-plate) (7.2 g), mercury(II) cyanide (1.35 g), and 2,3,4-tri-*O*-benzoyl-α-D-arabinopyranosyl bromide (77) [20] (1.65 g) were added. The mixture was stirred at 70—75 °C for 96 h. Additional bromo-sugar (77) (500 mg) was added and the reaction was continued for a further 48 h. The product was worked up as before and chromatographed on a silica gel dry column (600 g) using benzene–ether–methanol (49.5 : 49.5 : 1 v/v) as the eluant to give *O-2,3,4-tri-O-benzoyl-α-D-arabinopyranosyl-(1 ⟶ 6)-1,3,2′,6′-tetrakis-N-benzyloxycarbonylgentamine C_1* (78) (291 mg, 14%) as crystals from dichloromethane, (Found: C, 66.1; H, 5.9; N, 4.6. $C_{72}H_{74}N_4O_{19}$ requires C, 65.55; H, 5.7; N, 4.3%), δ_H [$CDCl_3$ – CD_3OD (3 : 1)] 1.15 (3 H, d, $J_{6',7'}$ 6 Hz, 7′-CH_3), 2.63 (3 H, s, 6′-NCH_3), 7.33br and 7.40br (20 H, 2 s, $-OCH_2C_6H_5$) and 7.50 and 7.90 (15 H, 2 m, Bz). The latter was dissolved in methanol (14.5 ml) and concentrated ammonium hydroxide (1.5 ml) was added. The mixture was stirred at 25 °C for 18 h. The material started to precipitate, whereupon chloroform (30 ml) and concentrated ammonium hydroxide (3 ml) were added and the reaction was then allowed to proceed for a further 96 h. The solution was evaporated to dryness and the residue was taken up in ethyl acetate (100 ml), washed with water (3 × 100 ml), dried (Na_2SO_4), and evaporated. The residue (194 mg) was dissolved in liquid ammonia (30 ml) at −70 °C. Sodium (400 mg) was added and the mixture was stirred for 2 h. The reaction was worked up as described for (70). The eluate was evaporated to dryness and chromatographed on silica gel (15 g) using the lower phase of a chloroform–methanol–concentrated ammonium hydroxide solution (1 : 1 : 1 v/v) as the eluant to give *O*-α-D-arabinopyranosyl-(1 ⟶ 6)-gentamine C_1 (79) (29 mg, 32%) as an amorphous solid, δ_H (D_2O) 1.18 (3 H, d, $J_{6',7'}$ 6 Hz, 7′-CH_3), 2.46 (3 H, s, 6′-NCH_3), 4.54 (1 H, d, $J_{1ax'',2ax''}$ 6 Hz, 1*ax*″-H), and 5.26 (1 H, d, $J_{1eq',2ax'}$ 4 Hz, 1*eq*′-H).

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