

## The Megalomicins. Part 7.<sup>1</sup> A Structural Revision by Carbon-13 Nuclear Magnetic Resonance and X-Ray Crystallography. Synthesis and Conformational Analysis of 3-Dimethylamino- and 3-Azido-D- and -L-hexopyranosides, and the Crystal Structure of 4''-O-(4-Iodobenzoyl)megalomicin A

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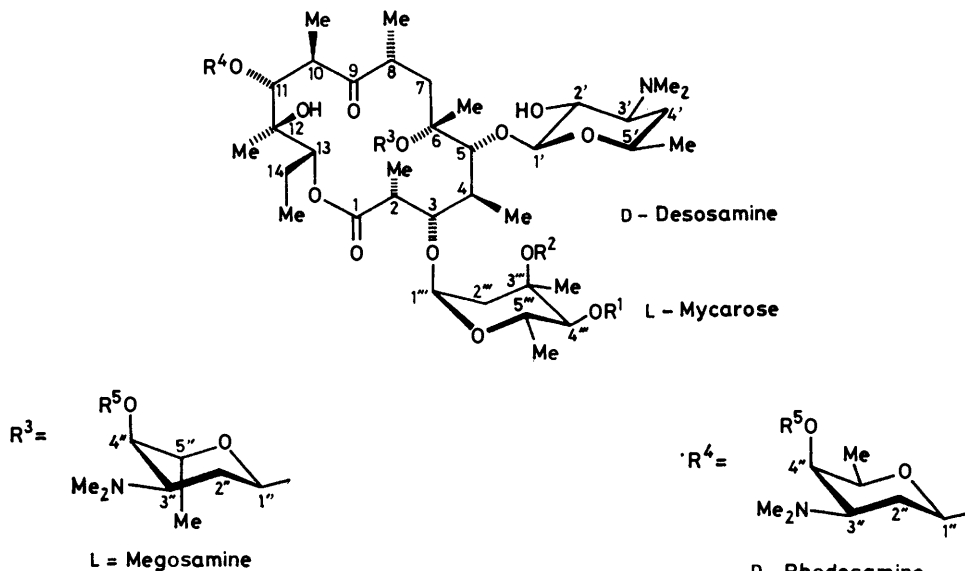
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An X-ray crystallographic study on 4''-O-(4-iodobenzoyl)megalomicin A has led to the revision of the structures of the megalomicins and the XK-41 antibiotics. Crystals are orthorhombic, space group  $P2_12_12_1$  with  $a = 12.669(2)$ ,  $b = 19.501(6)$ ,  $c = 25.741(9)$  Å, and  $Z = 4$ . The structure was solved by the heavy-atom technique, and 1 812 observed reflections led to a final  $R$  of 0.095. The novel amino-sugar previously thought to be D-rhososamine has been shown to have the L-configuration and is therefore renamed L-megosamine. It has also been shown to be glycosidically attached to the tertiary 6-hydroxy group. The  $^{13}\text{C}$  n.m.r. and circular dichroism (c.d.) parameters of these macrolides are described. The syntheses of methyl  $\alpha$ - and  $\beta$ -D-rhososaminide, methyl  $\alpha$ - and  $\beta$ -D-megosaminide, methyl  $\alpha$ - and  $\beta$ -L-megosaminide, methyl  $\alpha$ - and  $\beta$ -D-angolosaminide, and methyl 2,3,6-trideoxy-3-(dimethylamino)- $\alpha$ -D-xylo-hexopyranoside are described and their conformations and  $^{13}\text{C}$  n.m.r. parameters are discussed. Methyl  $\alpha$ -D- and -L-amicetoside, methyl  $\alpha$ -D- and -L-cineruloside and other model 4-oxopyranosides and pyrans have been synthesized. Their c.d. properties have been determined and they have been shown to exhibit Anti-Octant behaviour.

PREVIOUS independent studies on the megalomicins produced by *Micromonospora megalomicea* sp. n.<sup>2</sup> and on the XK-41 complex produced by *Micromonospora inositola* nov. sp.,<sup>3</sup> have led to the assignment of structures for megalomicin A<sup>4-6</sup> (XK-41-C)<sup>7</sup> (1), megalomicin B<sup>4-6</sup>

(XK-41-B<sub>1</sub>)<sup>7</sup> (2), megalomicin C<sub>1</sub><sup>4-6</sup> (XK-41-A<sub>2</sub>)<sup>7</sup> (3), megalomicin C<sub>2</sub><sup>4-6</sup> (XK-41-A<sub>1</sub>)<sup>7</sup> (4), and XK-41-B<sub>2</sub><sup>7</sup> (5). The novel amino-sugar present in these antibiotics was thought to be D-rhososamine.<sup>8,9</sup> Subsequently the  $^{13}\text{C}$  n.m.r. data for megalomicin A (1) were published<sup>10</sup>



### Revised Structure

- (1) R<sup>1</sup> = R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = H,
- (2) R<sup>1</sup> = Ac, R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = H,
- (3) R<sup>1</sup> = R<sup>2</sup> = Ac, R<sup>4</sup> = R<sup>5</sup> = H,
- (4) R<sup>1</sup> = COEt, R<sup>2</sup> = Ac, R<sup>4</sup> = R<sup>5</sup> = H,
- (5) R<sup>1</sup> = COEt, R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = H,
- (6) R<sup>1</sup> = R<sup>2</sup> = R<sup>4</sup> = H, R<sup>5</sup> = COC<sub>6</sub>H<sub>4</sub>I-*p*,

### Original Structure

- (1) R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = R<sup>5</sup> = H,
- (2) R<sup>1</sup> = Ac, R<sup>2</sup> = R<sup>3</sup> = R<sup>5</sup> = H,
- (3) R<sup>1</sup> = R<sup>2</sup> = Ac, R<sup>3</sup> = R<sup>5</sup> = H,
- (4) R<sup>1</sup> = COEt, R<sup>2</sup> = Ac, R<sup>3</sup> = R<sup>5</sup> = H,
- (5) R<sup>1</sup> = COEt, R<sup>2</sup> = R<sup>3</sup> = R<sup>5</sup> = H,

TABLE I  
Carbon-13 chemical shifts (p.p.m. downfield from SiMe<sub>4</sub> in CDCl<sub>3</sub> unless otherwise stated)

## (a) 3-Dimethylamino-sugars

Carbon	(7)	(8)	(35)	(36)	(38)	(38) <sup>a,b</sup>	(38)-H <sup>+</sup> <sup>a</sup>	$\Delta\delta_C$ (38)→(38)-H <sup>+</sup>
C-1	98.1	101.6	98.7	102.2	99.3	101.0	99.8	-1.2
C-2	28.5	30.7	25.7	27.1	28.9	29.4	27.8	-1.6
C-3	59.8	64.3	61.7	65.6	56.0	57.0	60.0	+3.0
C-4	66.1	65.8	71.7	71.3	67.6	69.6	66.5	-3.1
C-5	65.2	71.5	69.0	73.6	72.9	76.6	76.5	-0.1
C-6	17.1	17.0	18.3	18.3	19.7	20.2	20.0	-0.2
1-OMe	54.7	56.2	54.6	56.5	55.2	55.5	55.6	+0.1
3-NMe <sub>2</sub>	42.1	42.4	40.0	40.3	42.4	42.7	41.7/ 41.2	-1.0 -1.5

Carbon	(37)	(37) <sup>a,b</sup>	(37)-H <sup>+</sup> <sup>a</sup>	$\Delta\delta_C$ (37)→(37)-H <sup>+</sup>	(40)	$\Delta\delta_C$ (40)→(37)	(43)	(44)
C-1	98.2	99.4	98.0	-1.4	97.9	+0.3	104.6	105.8
C-2	28.8	29.8	28.7	-1.1	26.7	+2.1	29.1	32.9
C-3	60.0	61.1	63.4	+2.3	62.7	-2.7	67.8	64.8
C-4	70.8	73.7	71.7	-2.0	68.5	+2.3	79.3	84.9
C-5	68.6	70.2	68.7	-1.5	68.5	+0.1	70.9	70.3
C-6	18.6	18.1	17.8	-0.3	13.8	+4.8	19.8	19.2
1-OMe	55.2	55.7	55.8	+0.1	55.6	-0.4	55.1	54.8
3-NMe <sub>2</sub>	42.9	43.1	43.4/ 42.6	+0.3/ -0.5	41.2	+1.7	41.7	41.3

## (b) 3-Azido-sugars

Carbon	(21)	(27)	(18)	(24)	(32)	(34)
C-1	98.0	101.1	97.6	100.5	96.4	98.5
C-2	28.5	30.3	35.0	35.9	32.4	35.2
C-3	56.9	59.4	60.6	62.7	58.4	60.9
C-4	69.9	69.7	76.0	75.6	72.2	72.7
C-5	65.9	71.5	67.7	72.5	64.2	70.5
C-6	16.8	16.8	17.7	17.7	17.5	17.9
1-OMe	54.9	56.7	54.7	56.6	55.2	56.5

## (c) Mycarose derivatives

Carbon	(54)	(55)	(56)	(57)
C-1	98.6	99.5	97.8	99.1
C-2	41.5	43.3	36.0	39.4
C-3	69.8	70.9	78.3	81.1
C-4	77.3	77.8	77.7	77.4
C-5	62.9	68.2	62.6	68.1
C-6	17.4	17.7	17.3	17.7
1-OMe	55.1	56.4	55.1	56.3
3-Me	25.8	27.4	22.5 <sup>c</sup>	22.2
3-OCOMe			170.9	169.9
3-OCOMe			22.3 <sup>c</sup>	22.2
4-OCOR	170.7	170.0	174.0	173.9
4-OCOMe	20.9	20.8		
4-OCOCH <sub>2</sub> Me			27.6	27.6
4-OCOCH <sub>2</sub> Me			9.3	9.3

<sup>a</sup> Recorded in CD<sub>3</sub>OD. <sup>b</sup> Assignments confirmed by incremental titration from neat CDCl<sub>3</sub> to CD<sub>3</sub>OD in increments of ca. 10%.  
<sup>c</sup> Values may be interchanged within any vertical column.

and several anomalies,\* namely the chemical shifts of C-12 ( $\delta_C$  80.8) and C1'' † ( $\delta_C$  90.8), as well as C-2''' ( $\delta_C$  37.6), C-5''' ( $\delta_C$  67.7), 3'''-Me ( $\delta_C$  19.2),<sup>11</sup> C-3''' ( $\delta_C$  66.0) and C-5'' ( $\delta_C$  59.9) were apparent to us.

A tertiary glycosidic linkage of rhodosamine appeared reasonable in megalomicin A (1) in view of the shielding of C-1''<sup>12,13</sup> and of the 6-methyl group<sup>10,14,15</sup> but could not be accommodated at C-6 if the original mass-spectral data<sup>6</sup> and hydrogen-bonding proposals involving the 6-hydroxy and 9-carbonyl groups<sup>10</sup> were correct. An axial linkage for the glycoside was also impossible from rotational considerations<sup>4,5</sup> and was in disagreement with the  $J(^{13}\text{C}-^1\text{H})$  coupling constant (158 Hz) that we measured for C-1'' of (2).<sup>16,17</sup>

\* It should be noted that these assignments were made without access to any of the megalomicin degradation products, and were interpreted with reference to an erroneous structure.

## RESULTS AND DISCUSSION

In order to explain some of these anomalies, methyl  $\alpha$ -D-rhodosaminide (7) and its  $\beta$ -anomer (8) were synthesized in the following manner starting from 2-deoxy-D-glucose (9). The methyl  $\alpha$ -D-glycoside (10) of (9) was converted into the benzylidene derivative (11) in the usual way and the latter was oxidized with ruthenium tetroxide to give the ketone (12). Reduction with sodium borohydride afforded the alcohol (13) which after conversion to the methanesulphonate (14),<sup>18</sup> was treated with *N*-bromosuccinimide to give the bromo-sugar (15). Catalytic reduction afforded the 6-deoxy-sugar (16) which was converted into the azide (17) and

† To conform with current macrolide antibiotic nomenclature practices, (*R*)-*O*-glycosides are given precedence over (*S*)-*O*-glycosides, thus establishing the precedent desosamine ('), megosamine (''), and mycarose ('').

then hydrolysed with sodium methoxide to give the alcohol (18). Epimerization of C-4 was now achieved by conversion of (18) into the methanesulphonate (19) followed by displacement with sodium benzoate to give (20) and hydrolysis with sodium methoxide to give the alcohol (21). Reductive formylation of the latter afforded methyl  $\alpha$ -D-rhodosaminide (7). Equilibration of (16) with methanolic hydrogen chloride followed by chromatography of the product gave the  $\beta$ -anomer (22). This was converted into the azide (23), which on treatment with sodium methoxide gave the alcohol (24). Epimerization of C-4 was effected as before by conversion into the methanesulphonate (25), followed by displacement with sodium benzoate to give (26), and hydrolysis with sodium methoxide to give the alcohol (27). Reductive formylation of the latter afforded methyl  $\beta$ -D-rhodosaminide (8).

Direct comparison of the specific rotations and  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. spectra (Table 1) of the synthetic methyl  $\alpha$ -D-rhodosaminide (7) and its  $\beta$ -anomer (8) with those of the natural glycosides,<sup>8,9</sup> showed that the substances were different. An X-ray crystallographic study was therefore undertaken. Initial attempts using crystalline XK-41-B<sub>1</sub> (2),\* or megalomicin A (1) failed to give acceptable diffraction data due to the formation of symmetrical dimers. Consequently 4''-O-(4-iodobenzoyl)megalomicin A (6) was synthesized from megalomicin A (1) by controlled acylation using 4-iodobenzoyl chloride. The mass spectrum of (6) clearly indicated, from the fragment ions at  $m/e$  978(ff), 801(o), 719(j), 718(i), 703(l), 702(k), 657(p), 388(n), 158(m), and 145(cc), that the iodobenzoate was at the 4''-position.<sup>6</sup> Several crystallizations from aqueous acetone afforded suitable

crystals for the X-ray study, which afforded the crystallographic data given in Tables 2—4.

TABLE 2

Fractional co-ordinates ( $\times 10^3$ ) for 4''-O-(4-iodobenzoyl)-megalomicin A (6) (estimated standard deviations in parentheses)

Atom	$x/a$	$y/b$	$z/c$
I	829(3)	649(1)	320(1)
O(1)	179(22)	359(12)	265(7)
O(2)	411(19)	425(12)	378(7)
O(3)	-48(22)	521(12)	99(8)
O(4)	39(19)	416(10)	376(7)
O(5)	318(21)	515(10)	349(7)
O(6)	56(23)	293(12)	163(9)
O(7)	406(27)	474(15)	519(7)
O(8)	140(13)	570(10)	198(7)
O(9)	103(20)	425(11)	114(8)
O(10)	647(23)	305(12)	319(13)
O(11)	532(19)	353(15)	260(9)
O(12)	326(23)	325(10)	304(8)
O(13)	349(32)	580(14)	443(11)
O(14)	84(20)	345(13)	445(8)
O(15)	-71(26)	509(15)	449(9)
O(16)	280(19)	503(11)	181(10)
N(1)	493(32)	315(27)	158(12)
N(2)	-134(31)	458(24)	545(16)
C(1)	235(33)	539(16)	208(16)
C(2)	267(32)	559(18)	265(12)
C(3)	261(30)	494(16)	303(12)
C(4)	146(30)	434(18)	316(14)
C(5)	127(29)	414(18)	343(10)
C(6)	106(28)	350(21)	309(10)
C(7)	-2(30)	357(18)	285(13)
C(8)	-22(40)	303(20)	246(14)
C(9)	-6(38)	328(28)	190(20)
C(10)	-54(41)	392(18)	164(17)
C(11)	38(31)	445(18)	159(13)
C(12)	-6(31)	522(15)	147(9)
C(13)	96(34)	565(15)	147(10)
C(14)	78(39)	641(21)	130(14)
C(15)	178(46)	678(19)	121(16)
C(16)	388(31)	579(20)	253(15)
C(17)	100(36)	543(19)	349(20)
C(18)	126(29)	284(15)	334(12)
C(19)	-145(32)	278(23)	239(15)
C(20)	112(29)	372(20)	114(14)
C(21)	-87(29)	545(17)	185(13)
C(1')	54(33)	417(16)	427(15)
C(2')	-48(36)	440(22)	456(16)
C(3')	-38(45)	425(27)	521(17)
C(4')	-0(50)	348(25)	529(19)
C(5')	111(37)	338(32)	504(15)
C(6')	136(45)	259(24)	508(20)
C(7')	-222(48)	420(34)	538(25)
C(8')	-103(85)	474(39)	606(17)
C(1'')	260(36)	313(18)	260(11)
C(2'')	329(38)	332(16)	210(13)
C(3'')	424(39)	292(21)	206(19)
C(4'')	480(42)	284(18)	263(20)
C(5'')	416(34)	279(23)	310(14)
C(6'')	388(33)	203(21)	315(15)
C(7'')	458(99)	296(32)	132(33)
C(8'')	576(47)	251(30)	152(20)
C(9'')	612(39)	352(22)	296(17)
C(10'')	670(37)	424(21)	299(16)
C(11'')	645(33)	476(24)	263(15)
C(12'')	673(49)	545(26)	268(17)
C(13'')	755(30)	550(19)	310(18)
C(14'')	786(37)	499(22)	347(18)
C(15'')	-262(28)	434(18)	342(13)
C(1''')	426(32)	488(18)	352(13)
C(2''')	490(31)	537(22)	380(14)
C(3''')	458(33)	546(18)	438(20)
C(4''')	450(36)	474(20)	465(14)
C(5''')	382(30)	427(17)	431(16)
C(6''')	382(35)	354(22)	453(14)
C(7''')	539(48)	591(24)	470(19)

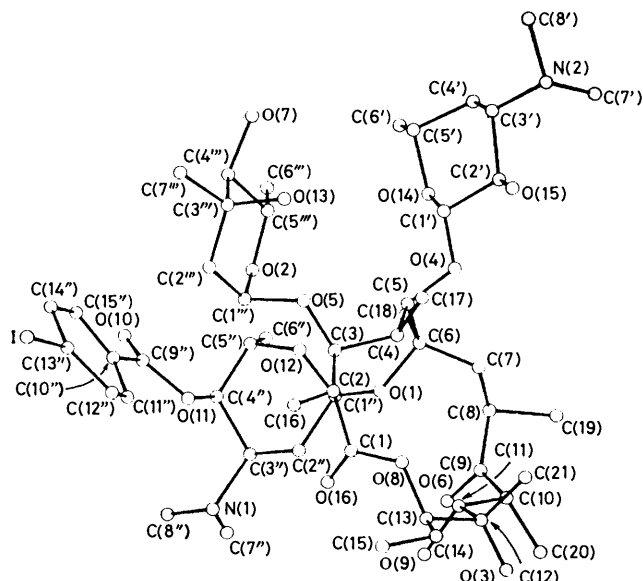


FIGURE 1 X-Ray structure of 4''-O-(4-iodobenzoyl)-megalomicin A (6) (hydrogen atoms are omitted)

\* The sample was kindly supplied to one of us (G. L.) by Dr. T. Nara, Kyowa Hakko Kogyo Co. Ltd.

TABLE 3

Bond lengths (Å) in 4''-O-(4-iodobenzoyl)-megalomicin A(6) (estimated standard deviations in parentheses)

C(1)-C(2)	1.58(0.051)	N(2)-C(8')	1.46(0.066)
C(1)-O(16)	1.13(0.045)	C(4')-C(5')	1.56(0.076)
C(1)-O(8)	1.37(0.045)	C(5')-C(6')	1.59(0.077)
C(2)-C(3)	1.59(0.046)	C(5')-O(14)	1.60(0.044)
C(2)-C(16)	1.62(0.055)	C(1'')-C(2'')	1.59(0.052)
C(3)-C(4)	1.51(0.053)	C(1'')-O(1)	1.38(0.049)
C(3)-O(5)	1.45(0.039)	C(1'')-O(12)	1.42(0.042)
C(4)-C(5)	1.55(0.049)	C(2'')-C(3'')	1.44(0.064)
C(4)-C(17)	1.54(0.056)	C(3'')-C(4'')	1.64(0.072)
C(5)-C(6)	1.56(0.048)	C(3'')-N(1)	1.56(0.060)
C(5)-O(4)	1.39(0.040)	N(1)-C(7'')	0.88(0.100)
C(6)-C(7)	1.50(0.051)	N(1)-C(8'')	1.63(0.076)
C(6)-C(18)	1.47(0.048)	C(4'')-C(5'')	1.47(0.065)
C(6)-O(1)	1.46(0.038)	C(4'')-O(11)	1.49(0.049)
C(7)-C(8)	1.48(0.051)	O(11)-C(9'')	1.37(0.052)
C(8)-C(9)	1.52(0.064)	C(9'')-C(10'')	1.58(0.061)
C(8)-C(19)	1.64(0.064)	C(9'')-O(10)	1.19(0.052)
C(9)-C(10)	1.53(0.067)	C(10'')-C(11'')	1.42(0.058)
C(9)-O(6)	1.27(0.058)	C(10'')-C(15'')	1.42(0.060)
C(10)-C(11)	1.57(0.059)	C(11'')-C(12'')	1.38(0.069)
C(10)-C(20)	1.53(0.060)	C(12'')-C(13'')	1.51(0.069)
C(11)-C(12)	1.63(0.047)	C(13'')-C(14'')	1.45(0.062)
C(11)-O(9)	1.47(0.042)	C(13'')-I	2.16(0.038)
C(12)-C(13)	1.54(0.054)	C(14'')-C(15'')	1.42(0.056)
C(12)-C(21)	1.49(0.047)	C(5'')-C(6'')	1.53(0.060)
C(12)-O(3)	1.35(0.033)	C(5'')-O(12)	1.47(0.050)
C(13)-C(14)	1.55(0.050)	C(1'')-C(2'')	1.46(0.054)
C(13)-O(8)	1.45(0.034)	C(1'')-O(5)	1.47(0.048)
C(14)-C(15)	1.48(0.071)	C(1'')-O(2)	1.42(0.041)
C(1')-C(2')	1.56(0.060)	C(2'')-C(3'')	1.54(0.063)
C(1')-O(4)	1.33(0.043)	C(3'')-C(4'')	1.55(0.055)
C(1')-O(14)	1.53(0.040)	C(3'')-C(7'')	1.59(0.069)
C(2')-C(3')	1.71(0.060)	C(3'')-O(13)	1.54(0.057)
C(2')-O(15)	1.39(0.052)	C(4'')-C(5'')	1.54(0.055)
C(3')-C(4')	1.58(0.072)	C(4'')-O(7)	1.48(0.044)
C(3')-N(2)	1.50(0.068)	C(5'')-C(6'')	1.52(0.054)
N(2)-C(7')	1.34(0.076)	C(5'')-O(2)	1.41(0.044)

The X-ray crystal structure of (6) (Figure 1) indicated that the absolute stereochemistry at C-5'' was L and not D as originally deduced. It is therefore proposed that this sugar be renamed L-megosamine [2,3,6-tri-deoxy-3-(dimethylamino)-L-ribo-hexose]. The X-ray study also revealed that the L-megosamine was glycosidically attached to the tertiary 6-hydroxy- group. With this important data it was possible to clarify the <sup>13</sup>C n.m.r. anomalies and to explain why the original conclusions had led to the incorrect structure.

The original <sup>1</sup>H n.m.r. assignments (60 MHz)<sup>8,9</sup> for methyl α-L-megosaminide (37) and the β-anomer (38) were verified at 100 MHz and all assignments (Table 5) were confirmed by double-resonance experiments. The small *J*(4,5) coupling was consistent with both the original and the revised structures and did not enable them to be distinguished. In addition to the W-coupling noted previously<sup>8,9</sup> for H-2e and H-4e in the α-anomer (37), it was possible at 100 MHz to observe W-coupling between H-2e and H-4e in the β-anomer (38) as well. It was also interesting to note that in (38) H-2a was deshielded (δ<sub>H</sub> 1.97) while H-2e was shielded (δ<sub>H</sub> 1.80) due to the axial 1-OMe group. A similar observation has been made for methyl 3-N-acetyl-4-O-acetylristosaminide which adopts a <sup>1</sup>C<sub>4</sub> conformation in which H-2a is deshielded by the *trans*-diaxial groups at C-1 and C-3 in the molecule.<sup>19</sup> The observed coupling constants clearly supported a <sup>4</sup>C<sub>1</sub> conformation for the α-anomer (37) and possibly a somewhat flattened

<sup>4</sup>C<sub>1</sub> conformation for the β-anomer (38) due to steric repulsion between the axial 5-Me and 1-OMe groups in the latter. The circular dichroism (c.d.) data in tetra-amine-copper solution for the α-anomer (37) ([θ]<sub>285</sub> - 5 380) and the β-anomer (38) ([θ]<sub>290</sub> - 5 420) supported these conclusions. There are numerous examples in the literature<sup>20-22</sup> where sugars have been shown to adopt conformations having the 5-Me, or 5-CH<sub>2</sub>OH substituents equatorial and all other substituents, even bulky ones, axial, in spite of the 1,3-diaxial interactions so produced. Only one sugar has been reported to date to adopt a flipped conformation in which the 5-substituent becomes axially oriented, namely methyl 3-N-benzoyl-4-O-benzoyl-β-D-ristosaminide (39), which adopts

TABLE 4

Bond angles (°) in 4''-O-(4-iodobenzoyl)megalomicin A(6) (estimated standard deviations in parentheses)

O(8)-C(1)-C(2)	106(2.9)	N(2)-C(3')-C(4')	127(4.4)
O(8)-C(1)-O(16)	128(3.7)	C(3')-N(2)-C(7')	113(4.6)
O(16)-C(1)-C(2)	126(3.7)	C(3')-N(2)-C(8')	106(4.7)
C(1)-C(2)-C(3)	111(2.7)	C(7')-N(2)-C(8')	116(5.2)
C(1)-C(2)-C(16)	97(2.7)	C(3')-C(4')-C(5')	110(4.3)
C(16)-C(2)-C(3)	111(3.0)	C(4')-C(5')-C(6')	106(4.1)
C(2)-C(3)-C(4)	107(2.9)	C(4')-C(5')-O(14)	100(3.3)
C(2)-C(3)-O(5)	104(2.5)	C(6')-C(5')-O(14)	101(3.5)
C(3)-C(4)-C(5)	110(2.6)	C(5')-O(14)-C(1')	116(3.0)
C(3)-O(5)-C(1'')	115(2.3)	O(1)-C(1'')-O(12)	104(2.4)
C(3)-C(4)-C(5)	112(2.9)	O(1)-C(1'')-C(2'')	110(2.7)
C(3)-C(4)-C(17)	113(3.0)	O(12)-C(1'')-C(2'')	106(3.3)
C(17)-C(4)-C(5)	110(3.0)	C(1'')-C(2'')-C(3'')	113(3.2)
C(4)-C(5)-C(6)	118(2.4)	C(2'')-C(3'')-C(4'')	110(3.7)
C(4)-C(5)-O(4)	113(2.8)	C(2'')-C(3'')-N(1)	112(3.6)
C(5)-O(4)-C(1')	118(2.7)	N(1)-C(3'')-C(4'')	119(3.8)
O(4)-C(5)-C(6)	103(2.7)	C(3'')-N(1)-C(7'')	101(7.7)
C(5)-C(6)-C(7)	108(3.0)	C(3'')-N(1)-C(8')	103(3.6)
C(5)-C(6)-C(18)	115(2.4)	C(7'')-N(1)-C(8'')	8.6(7.4)
C(5)-C(6)-O(1)	104(2.7)	C(3'')-C(4'')-C(5'')	121(4.2)
C(18)-C(6)-C(7)	114(3.2)	C(3'')-C(4'')-O(11)	94(3.0)
C(18)-C(6)-O(1)	10(2.9)	O(11)-C(4'')-C(5'')	110(3.4)
O(1)-C(6)-C(7)	105(2.3)	C(4'')-O(11)-C(9'')	107(3.2)
C(6)-O(1)-C(1'')	119(2.5)	O(11)-C(9'')-C(10'')	112(3.4)
C(6)-C(7)-C(8)	112(3.3)	O(11)-C(9'')-O(10)	128(4.0)
C(7)-C(8)-C(9)	114(3.5)	O(10)-C(9'')-C(10'')	119(4.0)
C(7)-C(8)-C(19)	116(3.5)	C(9'')-C(10'')-C(11'')	120(3.7)
C(19)-C(8)-C(9)	97(3.2)	C(9'')-C(10'')-C(15'')	116(3.4)
C(8)-C(9)-C(10)	128(4.2)	C(10'')-C(11'')-C(12'')	126(4.0)
C(8)-C(9)-O(6)	116(4.2)	C(11'')-C(12'')-C(13'')	108(3.9)
O(6)-C(9)-C(10)	116(4.2)	C(12'')-C(13'')-C(14'')	128(3.7)
C(9)-C(10)-C(11)	106(3.8)	C(12'')-C(13'')-I	117(3.0)
C(9)-C(10)-C(20)	111(3.4)	I-C(13'')-C(14'')	115(3.0)
C(20)-C(10)-C(11)	116(3.4)	C(13'')-C(14'')-C(15'')	117(3.9)
C(10)-C(11)-C(12)	112(3.1)	C(14'')-C(15'')-C(10'')	117(3.6)
C(10)-C(11)-O(9)	108(2.8)	C(15'')-C(10'')-C(11'')	123(3.7)
O(9)-C(11)-C(12)	106(2.4)	C(4'')-C(5'')-C(6'')	105(3.2)
C(11)-C(12)-C(13)	103(2.9)	C(4'')-C(5'')-O(12)	107(3.2)
C(11)-C(12)-C(21)	113(2.4)	C(6'')-C(5'')-O(12)	115(3.3)
C(11)-C(12)-O(3)	107(2.3)	C(5'')-O(12)-C(1'')	117(2.6)
C(21)-C(12)-O(3)	110(3.1)	O(5)-C(1'')-O(2)	102(2.7)
C(21)-C(12)-C(13)	115(2.5)	O(5)-C(1'')-C(2'')	108(2.9)
O(3)-C(12)-C(13)	110(2.3)	O(2)-C(1'')-C(2'')	114(2.9)
C(12)-C(13)-C(14)	114(3.3)	C(1'')-C(2'')-C(3'')	114(3.3)
C(12)-C(13)-O(8)	111(2.2)	C(2'')-C(3'')-C(4'')	110(3.2)
C(13)-C(14)-C(15)	113(3.8)	C(2'')-C(3'')-C(7'')	113(3.6)
C(13)-O(8)-C(1)	118(2.6)	C(7'')-C(3'')-C(4'')	107(3.7)
O(8)-C(13)-C(14)	104(2.4)	C(2'')-C(3'')-O(13)	112(3.5)
O(4)-C(1')-O(14)	109(2.5)	O(13)-C(3'')-C(4'')	107(3.3)
O(4)-C(1')-C(2')	111(3.2)	C(3'')-C(4'')-C(5'')	108(3.2)
C(1')-C(2')-C(3')	112(3.5)	C(3'')-C(4'')-O(7)	116(3.3)
C(1')-C(2')-O(15)	113(3.3)	O(7)-C(4'')-C(5'')	109(3.3)
O(14)-C(1')-C(2')	108(2.9)	C(4'')-C(5'')-C(6'')	111(3.2)
O(15)-C(2')-C(3')	109(3.2)	C(4'')-C(5'')-O(2)	115(3.0)
C(2')-C(3')-C(4')	108(3.5)	C(6'')-C(5'')-O(2)	109(2.8)
C(2')-C(3')-N(2)	106(3.7)	C(5'')-O(2)-C(1'')	119(2.4)

TABLE 5

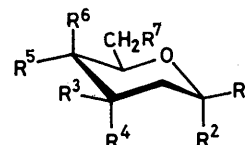
Hydrogen-1 chemical shifts and coupling constants (p.p.m. downfield from SiMe<sub>4</sub> in CDCl<sub>3</sub>, measured at 100 MHz)

Compound	Atom	$\delta_H$	Multiplicity	Coupling constants/ Hz	
(37)	H <sub>1a</sub>	4.68	dd	$J_{1a,2a}$ 8, $J_{1a,2e}$ 5	
	H <sub>2e</sub>	2.01	dddd	$J_{1a,2e}$ 5, $J_{2e,2a}$ 12.5, $J_{2e,3a}$ 4.5, $J_{2e,4e}$ 1*	
	H <sub>2a</sub>	1.61	ddd	$J_{1a,2a}$ 8, $J_{2e,2a}$ 12.5, $J_{2a,3a}$ 12.5	
	H <sub>3a</sub>	2.35	ddd	$J_{2e,3a}$ 4.5, $J_{2a,3a}$ 12.5, $J_{3a,4e}$ 4.5	
	H <sub>4e</sub>	3.60	ddd	$J_{3a,4e}$ 4.5, $J_{4e,5e}$ 5, $J_{2e,4e}$ 1*	
	H <sub>5e</sub>	3.97	dq	$J_{4e,5e}$ 5, $J_{5e,6}$ 7	
	1-OMe	3.40	s		
	3-NMe <sub>2</sub>	2.34	s		
	5-Me	1.30	d	$J_{5e,6}$ 7	
	4-OH	4.25	s		
	(38)	H <sub>1e</sub>	4.83	dd	$J_{1e,2e}$ 2.5, $J_{1e,2a}$ 3.5
		H <sub>2e</sub>	1.80	dddd	$J_{1e,2e}$ 2.5, $J_{2e,2a}$ 12.5, $J_{2e,3a}$ 6.5, $J_{2e,4e}$ ca. 1*
		H <sub>2a</sub>	1.97	ddd	$J_{1e,2a}$ 3.5, $J_{2e,2a}$ 12.5, $J_{2a,3a}$ 10
H <sub>3a</sub>		2.68	ddd	$J_{2e,3a}$ 6.5, $J_{2a,3a}$ 10, $J_{3a,4e}$ 3	
H <sub>4e</sub>		3.74	ddd	$J_{3a,4e}$ = $J_{4e,5e}$ 2.5, $J_{2e,4e}$ ca. 1*	
H <sub>5e</sub>		4.12	dq	$J_{4e,5e}$ 2.5, $J_{5e,6}$ 7	
1-OMe		3.41	s		
3-NMe <sub>2</sub>		2.34	s		
5-Me		1.37	d	$J_{5e,6}$ 7	
4-OH		3.65	s		
(40)		H <sub>1a</sub>	4.70	dd	$J_{1a,2e}$ 4, $J_{1a,2a}$ 8
		H <sub>2e</sub>	2.02	ddd	$J_{1a,2e}$ = $J_{2e,3a}$ = 4, $J_{2e,2a}$ 13
		H <sub>2a</sub>	1.51	ddd	$J_{1a,2a}$ 8, $J_{2e,2a}$ 13, $J_{2a,3a}$ 11
	H <sub>3a</sub>	2.63	ddd	$J_{2e,3a}$ 4, $J_{2a,3a}$ 11, $J_{3a,4a}$ 8	
	H <sub>4a</sub>	3.72	dd	$J_{3a,4a}$ 8, $J_{4a,5e}$ 5	
	H <sub>5e</sub>	4.31	dq	$J_{4a,5e}$ 5, $J_{5e,6}$ 7	
	1-OMe	3.42	s		
	3-NMe <sub>2</sub>	2.36	s		
	5-Me	1.26	d	$J_{5e,6}$ 7	
	4-OH	3.20	s		

\* W-Coupling.

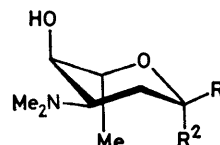
a <sup>1</sup>C<sub>4</sub> conformation.<sup>23</sup> The methyl L-megosaminides (37) and (38) constitute further examples.

The <sup>13</sup>C n.m.r. parameters for the methyl L-megosaminides (37) and (38) are unique and there are no comparative data in the literature for pyranosides having an axial 5-substituent. The <sup>13</sup>C chemical shifts for the pyranosides (37) and (38) as well as their furanoside forms (43) and (44) are given in Table 1. The shielding of C-1 in the  $\alpha$ -anomer (37) may be attributed to steric interaction between the axial 5-Me group and H-1. Additionally it is difficult to predict where C-1 would occur in the  $\beta$ -anomer (38) due to the presumed flattening of the chair. In megalomicin A (1) the anomeric carbon of L-megosamine is further shielded to  $\delta_C$  90.4 due to the glycosidic attachment of this sugar to the tertiary 6-OH group. In the  $\alpha$ -anomer (37) C-3 would be expected to be shielded by the axial 5-Me group and it occurs upfield ( $\delta_C$  60.0) relative to methyl  $\beta$ -D-rhodosaminide (8) ( $\delta_C$  64.3) and methyl  $\beta$ -D-desosaminide<sup>14</sup> ( $\delta_C$  65.4). Similar shielding would be expected in the case of the  $\beta$ -anomer where C-3 is further shielded to  $\delta_C$  56.0 due to the axial 1-OMe group relative to



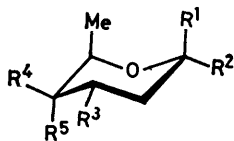
- (7) R<sup>1</sup> = R<sup>4</sup> = R<sup>5</sup> = R<sup>7</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = NMe<sub>2</sub>, R<sup>6</sup> = OH  
 (8) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = R<sup>7</sup> = H, R<sup>3</sup> = NMe<sub>2</sub>, R<sup>6</sup> = OH  
 (9) R<sup>1</sup>R<sup>2</sup> = H, OH, R<sup>3</sup> = R<sup>5</sup> = R<sup>7</sup> = OH, R<sup>4</sup> = R<sup>6</sup> = H  
 (10) R<sup>1</sup> = R<sup>4</sup> = R<sup>6</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = R<sup>5</sup> = R<sup>7</sup> = OH  
 (11) R<sup>1</sup> = R<sup>4</sup> = R<sup>6</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = OH, R<sup>5</sup>, R<sup>7</sup> = PhCH<O-  
 (12) R<sup>1</sup> = R<sup>6</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> and R<sup>4</sup> = =O, R<sup>5</sup>R<sup>7</sup> = PhCH<O-  
 (13) R<sup>1</sup> = R<sup>3</sup> = R<sup>6</sup> = H, R<sup>2</sup> = OMe, R<sup>4</sup> = OH, R<sup>5</sup>, R<sup>7</sup> = PhCH<O-  
 (14) R<sup>1</sup> = R<sup>3</sup> = R<sup>6</sup> = H, R<sup>2</sup> = OMe, R<sup>4</sup> = OSO<sub>2</sub>Me, R<sup>5</sup>, R<sup>7</sup> = PhCH<O-  
 (15) R<sup>1</sup> = R<sup>3</sup> = R<sup>6</sup> = H, R<sup>2</sup> = OMe, R<sup>4</sup> = OSO<sub>2</sub>Me, R<sup>5</sup> = OCOPh, R<sup>7</sup> = Br  
 (16) R<sup>1</sup> = R<sup>3</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>2</sup> = OMe, R<sup>4</sup> = OSO<sub>2</sub>Me, R<sup>5</sup> = OCOPh  
 (17) R<sup>1</sup> = R<sup>4</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = N<sub>3</sub>, R<sup>5</sup> = OCOPh  
 (18) R<sup>1</sup> = R<sup>4</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = N<sub>3</sub>, R<sup>5</sup> = OH  
 (19) R<sup>1</sup> = R<sup>4</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = N<sub>3</sub>, R<sup>5</sup> = OSO<sub>2</sub>Me  
 (20) R<sup>1</sup> = R<sup>4</sup> = R<sup>5</sup> = R<sup>7</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = N<sub>3</sub>, R<sup>6</sup> = OCOPh  
 (21) R<sup>1</sup> = R<sup>4</sup> = R<sup>5</sup> = R<sup>7</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = N<sub>3</sub>, R<sup>6</sup> = OH  
 (22) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>3</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>4</sup> = OSO<sub>2</sub>Me, R<sup>5</sup> = OCOPh  
 (23) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>4</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>3</sup> = N<sub>3</sub>, R<sup>5</sup> = OCOPh  
 (24) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>4</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>3</sup> = N<sub>3</sub>, R<sup>5</sup> = OH  
 (25) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>4</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>3</sup> = N<sub>3</sub>, R<sup>5</sup> = OSO<sub>2</sub>Me  
 (26) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = R<sup>7</sup> = H, R<sup>3</sup> = N<sub>3</sub>, R<sup>6</sup> = OCOPh  
 (27) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = R<sup>7</sup> = H, R<sup>3</sup> = N<sub>3</sub>, R<sup>6</sup> = OH  
 (28) R<sup>1</sup> = R<sup>4</sup> = R<sup>6</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = OSO<sub>2</sub>Me, R<sup>5</sup>, R<sup>7</sup> = PhCH<O-  
 (29) R<sup>1</sup> = R<sup>4</sup> = R<sup>6</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = OSO<sub>2</sub>Me, R<sup>5</sup> = OCOPh, R<sup>7</sup> = Br  
 (30) R<sup>1</sup> = R<sup>4</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = OSO<sub>2</sub>Me, R<sup>5</sup> = OCOPh  
 (31) R<sup>1</sup> = R<sup>3</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>2</sup> = OMe, R<sup>4</sup> = N<sub>3</sub>, R<sup>5</sup> = OCOPh  
 (32) R<sup>1</sup> = R<sup>3</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>2</sup> = OMe, R<sup>4</sup> = N<sub>3</sub>, R<sup>5</sup> = OH  
 (33) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>3</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>4</sup> = N<sub>3</sub>, R<sup>5</sup> = OCOPh  
 (34) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>3</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>4</sup> = N<sub>3</sub>, R<sup>5</sup> = OH  
 (35) R<sup>1</sup> = R<sup>4</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = NMe<sub>2</sub>, R<sup>5</sup> = OH  
 (36) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>4</sup> = R<sup>6</sup> = R<sup>7</sup> = H, R<sup>3</sup> = NMe<sub>2</sub>, R<sup>5</sup> = OH

methyl  $\alpha$ -D-rhodosaminide (7) ( $\delta_C$  59.8) and methyl  $\alpha$ -D-desosaminide<sup>14</sup> ( $\delta_C$  60.3). The assignment of C-2 was unambiguous, while direct assignment of C-4 and C-5 in (37) and (38) in CDCl<sub>3</sub> was not possible. The



- (37) R<sup>1</sup> = OMe, R<sup>2</sup> = H  
 (38) R<sup>1</sup> = H, R<sup>2</sup> = OMe

spectra were therefore measured in  $\text{CDCl}_3$  and the solvent was then gradually changed over to  $\text{CD}_3\text{OD}$  by titration in approximately 10% increments. Careful addition of  $\text{DCl}$  then afforded the expected upfield  $\beta$ -shifts due to protonation of the 3-NMe<sub>2</sub> group at C-2 and



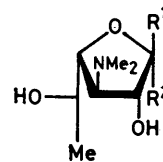
- (39) R<sup>1</sup> = OMe, R<sup>2</sup> = H, R<sup>3</sup> = NHCOPh,  
R<sup>4</sup> = H, R<sup>5</sup> = OCOPh  
(40) R<sup>1</sup> = R<sup>5</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = NMe<sub>2</sub>, R<sup>4</sup> = OH  
(41) R<sup>1</sup> = R<sup>4</sup> = H, R<sup>2</sup> = OMe, R<sup>3</sup> = NMe<sub>2</sub>, R<sup>5</sup> = OH  
(42) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>4</sup> = H, R<sup>3</sup> = NMe<sub>2</sub>, R<sup>5</sup> = OH

C-4, but not at C-5. The occurrence of the axial 5-Me signals at  $\delta_C$  18.6 in (37) and at  $\delta_C$  19.7 in (38) could not be rationalized without first determining the  $\gamma$ -anti-periplanar effect of the axial 4-OH group on these methyl groups.

Thus methyl 2,3,6-trideoxy-3-dimethylamino- $\alpha$ -D-xylo-hexopyranoside (40) was synthesized as a model compound. 2-Deoxy-D-galactose (45) was converted into the  $\alpha$ -methyl glycoside (46)<sup>24</sup> which was converted into the 4,6-O-benzylidene derivative (47)<sup>25</sup> by a modification<sup>26</sup> of the literature procedure. Treatment of the latter with methanesulphonyl chloride in pyridine afforded the 3-O-methanesulphonyl derivative (48), which was reacted with *N*-bromosuccinimide to give methyl 4-O-benzoyl-6-bromo-2,6-dideoxy-3-O-methanesulphonyl- $\alpha$ -D-lyxo-hexopyranoside (49). Reductive dehalogenation of (49) with tributylstannane yielded the deoxysugar (50). Displacement of the methanesulphonate in (50) with azide ion was accomplished with some difficulty, as expected, due to the presence of the axial 1-OMe group, to give methyl 3-azido-4-O-benzoyl-2,3,6-trideoxy- $\alpha$ -D-xylo-hexopyranoside (51). The <sup>1</sup>H n.m.r. spectrum of (51) revealed coupling constants that were consistent with a <sup>4</sup>C<sub>1</sub> conformation for the molecule, having the groups at C-1, C-3, and C-4 axial and the 5-Me group equatorial. Saponification of (51) gave the alcohol (52) which was subjected to reductive formylation to give methyl 2,3,6-trideoxy-3-dimethylamino- $\alpha$ -D-xylo-hexopyranoside (40). The <sup>1</sup>H n.m.r. spectrum of (40) (Table 5) revealed coupling constants that were consistent with a <sup>1</sup>C<sub>4</sub> conformation for the molecule indicating that the ring had flipped upon introducing the bulky 3-NMe<sub>2</sub> group thereby placing the 5-Me group in an axial orientation. It is of interest to note the similarities between the <sup>13</sup>C chemical shifts of C-1 and C-3 for (40) relative to those of (37) (Table 1). The deshielding of the axial 5-Me group from  $\delta_C$  13.8 in (40) to  $\delta_C$  18.6 in (37) upon epimerization of the 4-OH group, indicated a loss of the  $\gamma$ -gauche interaction of  $\Delta\delta_C +4.8$  in this case. A similar effect would be expected for the  $\beta$ -glycoside (38). The downfield shift of the 5-Me group in (38) is due to the  $\delta$ -syn-axial interaction with the  $\beta$ -1-OMe group. A further contribution to this downfield shift may arise from

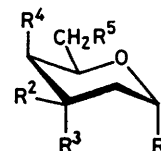
reduced axial character due to slight flattening of the ring.

With the above assignments in hand as well as those of methyl  $\alpha$ -L-mycaroside (53)<sup>11</sup> and methyl  $\alpha$ - and  $\beta$ -D-desosaminides,<sup>14</sup> it was necessary only to run the <sup>13</sup>C n.m.r. spectra of methyl 4-O-acetyl- $\alpha$ - and - $\beta$ -L-mycaro-



- (43) R<sup>1</sup> = OMe, R<sup>2</sup> = H  
(44) R<sup>1</sup> = H, R<sup>2</sup> = OMe

side, (54) and (55), as well as methyl 3-O-acetyl-4-O-propionyl- $\alpha$ - and - $\beta$ -L-mycaroside, (56) and (57) (Table 1), before attempting to assign the <sup>13</sup>C n.m.r. data for the megalomicins. The <sup>13</sup>C n.m.r. spectra of megalomicin A (1), megalomicin B (2), megalomicin C<sub>1</sub> (3), megalomicin C<sub>2</sub> (4), erythromycin A (58), megalalosamine (59), 2',4''-di-O-acetylmegalomicin B (60), (9S)-5-O- $\beta$ -D-desos-



- (45) R<sup>1</sup> = OH ( $\alpha$ ,  $\beta$ ), R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = OH, R<sup>3</sup> = H  
(46) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = OH, R<sup>3</sup> = H  
(47) R<sup>1</sup> = OMe, R<sup>2</sup> = OH, R<sup>3</sup> = H, R<sup>4</sup>, R<sup>5</sup> = PhCH<O-  
(48) R<sup>1</sup> = OMe, R<sup>2</sup> = OSO<sub>2</sub>Me, R<sup>3</sup> = H,  
R<sup>4</sup>, R<sup>5</sup> = PhCH<O-  
(49) R<sup>1</sup> = OMe, R<sup>2</sup> = OSO<sub>2</sub>Me, R<sup>3</sup> = H, R<sup>4</sup> = OCOPh, R<sup>5</sup> = Br  
(50) R<sup>1</sup> = OMe, R<sup>2</sup> = OSO<sub>2</sub>Me, R<sup>3</sup> = R<sup>5</sup> = H, R<sup>4</sup> = OCOPh  
(51) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>5</sup> = H, R<sup>3</sup> = N<sub>3</sub>, R<sup>4</sup> = OCOPh  
(52) R<sup>1</sup> = OMe, R<sup>2</sup> = R<sup>5</sup> = H, R<sup>3</sup> = N<sub>3</sub>, R<sup>4</sup> = OH

aminyl-9-dihydroerythronolide A (61), (9S)-9-dihydro-megalalosamine (62), (9S)-2',4'', 9,11-tetra-O-benzoyl-9-dihydromegalalosamine (63), 2',4''-di-O-benzoylmegalalosamine (64), 3-O-acetyl-2',4''-di-O-benzoylmegalalosamine (65), and 4''',9-di-O-acetyl-2'3''',4''-tri-O-propionylmegalomicin A-9, 12-hemiacetal (68) were recorded and the assignments are given in Table 6. Several points are worthy of comment.

The quasi-equatorial 6-Me group in erythromycin A (58)<sup>10,14,15</sup> occurs at  $\delta_C$  26.8 while the axial 12-Me group gives rise to a signal at  $\delta_C$  16.3. In megalomicin A (1), which has the L-megosamine glycosidically linked to the tertiary 6-OH group, the 6-Me group is shielded to  $\delta_C$  16.5. This upfield shift ( $\Delta\delta_C -10.3$ ) is greater than would have been anticipated simply from glycosylation of the tertiary 6-OH group. The X-ray study indicates that the 6-glycoside has a quasi-equatorial orientation thus forcing the 6-Me group to assume a quasi-axial orientation which would help to account for the additional upfield shift of this methyl group. Due to the presence of the glycoside, C-6 occurs at  $\delta_C$  80.4 in (1) relative to  $\delta_C$  74.9 in erythromycin A (58).<sup>10,14,15</sup> The

TABLE 6

Carbon-13 chemical shifts (p.p.m. downfield from SiMe<sub>4</sub> in CDCl<sub>3</sub>)<sup>a</sup>

Carbon	(1)	(2)	(3)	(4)	(58)	(59)	(60)	(61)	(62)	(63)	(64)	(65)	(68)
C-1	175.5(s)	175.5	175.8(s)	175.9(s)	175.9	176.0(s)	173.9	178.6(s)	176.5(s)	176.2(s)	174.1(s)	172.9	175.4(s)
C-2	44.8(d)	44.6	44.8(d)	44.8(d)	45.0	44.8(d)	44.5	44.5(d)	44.7(d)	43.4(d)	43.7(d)	42.7	38.9(d)
C-3	85.1(d)	82.2	81.8(d)	81.8(d)	80.2	77.5(d)	82.1	78.7(d)	77.5(d)	77.4(d)	75.9(d)	78.0	78.3(d)
C-4	37.2(d) e	37.2 d	37.2(d) d	37.2(d) d	38.2	35.9(d)	37.9 e	32.2(d)	37.4(d)	34.4(d)	36.1(d)	35.7	36.7(d)
C-5	82.9(d)	83.3	83.0(d)	83.0(d)	83.8	89.0(d)	82.4	96.6(d)	85.9(d)	83.0(d)	82.5(d)	80.4	82.8(d)
C-6	80.4(s)	80.3	80.1(s)	80.2(s)	74.9	80.3(s)	80.7	74.9(s)	83.0(s)	82.4(s)	80.7(s)	80.7	84.2(s) e
C-7	38.8(t)	38.7	39.0(t)	38.9(t)	38.6	38.1(t)	37.9 e	34.3(t)	35.8(t)	36.2(t)	37.4(t)	37.5	31.2(t)
C-8	45.8(d)	45.9	45.9(d)	45.9(d)	45.0	45.9(d)	45.6	38.2(d)	34.6(d)	39.2(d)	45.7(d)	45.6	40.7(d)
C-9	221.3(s)	221.5	221.4(s)	221.4(s)	221.3	221.2(s)	221.0	83.7(d)	83.1(d)	81.1(d)	221.1(s)	220.8	108.5(s)
C-10	37.7(d) e	37.5 d	37.4(d) d	37.4(d) d	39.4	37.4(d)	37.4	28.1(d)	32.5(d)	32.7(d)	37.4(d)	37.5	47.1(d)
C-11	68.8(d)	68.4	68.4(d)	68.4(d)	68.9	69.5(d)	68.8	70.1(d)	71.2(s)	73.5(d)	68.7(d)	69.3	85.8(d)
C-12	74.4(s)	74.4	74.4(s)	74.4(s)	74.9	74.3(s)	74.4	74.9(s)	74.8(s)	74.8(s)	74.3(s)	74.3	81.7(s) e
C-13	76.6(d)	77.6	76.6(d)	76.7(d)	77.0	77.2(d)	76.6	79.0(d)	77.1(d)	74.4(d)	76.8(d)	76.4	81.0(d)
C-14	21.2(t)	21.1	21.2(t)	21.2(t)	21.2	21.5(t)	21.6	20.9(t)	21.7(t)	23.1(t)	21.4(t)	21.4	24.0(t)
2-Me	18.8(q) e	18.8 e	18.8(q) e	18.8(q) e	18.7	18.3(q)	18.8	17.3(q)	21.4(q)	21.4(q)	18.4(q)	18.4	18.5(q)
4-Me	9.5(q)	9.7	9.8(q)	9.8(q)	9.2	8.6(q)	9.5	7.1(q)	8.4(q)	8.3(q)	7.9(q)	8.9	11.1(q)
6-Me	16.5(q) d	16.7 e	16.2(q)	16.3(q)	26.8	16.5(q)	16.5	21.0(q)	16.5(q)	15.9(q) e	16.5(q) e	16.5 e	16.5(q) d
8-Me	15.1(q)	15.1	15.0(q)	15.0(q)	15.9	15.5(q)	15.5	15.5(q) e	15.5(q)	15.6(q) e	15.2(q)	15.2	16.1(q)
10-Me	12.3(q)	12.4	12.4(q)	12.4(q)	12.0	12.7(q)	12.2	12.8(q)	15.5(q)	14.6(q)	12.4(q)	12.4	15.5(q)
12-Me	16.3(q) d	16.2 e	16.2(q)	16.3(q)	16.3	16.0(q) e	16.5	15.8(q) e	16.5(q)	15.4(q) e	16.0(q) e	16.3 e	25.8(q)
14-Me	10.4(q)	10.4	10.4(q)	10.4(q)	10.7	10.3(q)	10.5	11.0(q)	10.6(q)	10.8(q)	10.3(q)	10.3	11.1(q)
3-OCOMe												169.3	
3-OCOMe												21.4	
9-OCOMe													170.4(s) e
9-OCOMe													21.1(q) f
C-1'	104.5(d)	103.1	102.6(d)	102.5(d)	103.3	106.1(d)	100.2	106.2(d)	105.1(d)	100.7(d)	99.8(d)	100.1	101.1(d)
C-2'	71.2(d)	71.2	71.5(d)	71.4(d)	71.1	70.9(d)	72.0	70.7(d)	70.8(d)	71.0(d)	72.0(d)	72.0	72.0(d)
C-3'	65.4(d)	65.1	65.5(d)	65.5(d)	65.5	65.7(d)	63.6	65.3(d)	65.6(d)	63.1(d)	63.2(d)	63.8	63.9(d)
C-4'	28.6(t)	28.5	29.1(t)	29.0(t)	28.9	28.5(t)	30.9	28.1(t)	29.3(t)	32.0(t)	31.3(t)	31.7	30.8(t)
C-5'	69.2(d)	69.8	68.9(d)	68.9(d)	68.9	69.9(d)	69.8	69.8(d)	69.9(d)	70.2(e)	71.2(d)	71.0	70.3(d)
C-6'	21.5(q)	21.7	21.8(q)	21.8(q)	21.4	21.3(q)	21.6	21.0(q)	21.4(q)	21.1(q)	21.1(q)	20.9	21.2(q)
3'-NMe <sub>2</sub> b	40.2(q)	40.1	40.2(q)	40.2(q)	40.3	40.3(q)	40.6	40.2(q)	40.3(q)	40.5(q)	40.4(q)	40.8	40.7(q)
2'-OCOR								170.2 d			166.6(s) d	166.7 d	173.9(s) e
2'-OCOMe								21.6 e					
2'-OCOCH <sub>2</sub> Me													28.1(t) h
2'-OCOCH <sub>2</sub> Me													9.1(q)
C-1''	90.4(d)	90.3	90.4(d)	90.3(d)		90.8(d)	91.4		91.2(d)	91.6(d)	92.0(d)	91.8	91.8(d)
C-2''	27.9(t)	28.0	28.0(t)	28.0(t)		28.1(t)	28.7		28.6(t)	31.1(t)	28.9(t)	28.8	28.8(t)
C-3''	59.5(d)	59.4	59.4(d)	59.4(d)		59.3(d)	58.6		59.6(d)	58.6(d)	58.3(d)	58.6	58.7(d)
C-4''	73.5(d)	73.7	73.5(d)	73.6(d)		74.8(d)	72.0		73.2(d)	72.2(d)	72.6(d)	72.3	71.9(d)
C-5''	67.3(d)	67.3	67.5(d)	67.5(d)		68.1(d)	67.8		67.6(d)	68.9(d)	69.3(d)	69.3	68.7(d)
C-6''	18.6(q) e	18.8 e	18.8(q)	18.8(q) e		18.3(q)	18.8		20.3(q)	20.2(q)	18.6(q)	19.1	17.5(q)
3''-NMe <sub>2</sub> b	42.5(q)	42.5	42.5(q)	42.5(q)		42.4(q)	42.7		42.6(q)	42.2(q)	42.3(q)	42.2	42.3(q)
4''-OCOR								170.9 d				165.6(s) d	165.4 d
4''-OCOMe								21.6 e					174.0(q) g
4''-OCOCH <sub>2</sub> Me													27.9(t) h
4''-OCOCH <sub>2</sub> Me													9.1(q)
C-1'''	98.5(d)	97.9	97.5(d)	97.5(d)	96.4		98.3						98.8(d)
C-2'''	41.0(t)	41.5	36.4(t)	36.4(t)	35.1		41.5						35.7(t)
C-3'''	69.7(s)	69.5	78.0(s)	78.1(s)	72.7		69.5						78.1(s)
C-4'''	77.0(d)	77.2	78.0(d)	77.7(d)	78.2		77.1						78.3(d)
C-5'''	65.5(d)	63.1	62.7(d)	62.7(d)	65.6		62.8						62.9(d)
C-6'''	18.4(q) e	18.0 e	18.4(q) e	18.4(q) e	18.4		17.9						17.5(q)
3'''-Me	25.7(q)	25.7	23.1(q)	23.1(q)	21.5		25.8						22.6(q)
3'''-OMe					49.5								
3'''-OCOR			170.5(s) e	170.6(s)									172.8(s) g
3'''-OCOMe			22.8(q)	22.7(q)									
3'''-OCOCH <sub>2</sub> Me													28.1(t) h
3'''-OCOCH <sub>2</sub> Me													9.1(q)
4'''-OCOR		170.3	170.0(s) e	173.3(s)			170.2 d						170.3(s) e
4'''-OCOMe		20.8	20.7(q)				20.8 e						20.8(q) f
4'''-OCOCH <sub>2</sub> Me				27.7(t)									
4'''-OCOCH <sub>2</sub> Me				9.2(q)									

<sup>a</sup> The symbols in parentheses represent the multiplicities of the signals obtained in the SFORD spectrum. <sup>b</sup> The two Me groups gave one coincident signal in each case. <sup>c-h</sup> Values may be interchanged within any vertical column.

chemical shifts of C-11, C-12, and the 12-Me group in (1) occur unchanged relative to erythromycin A (58),<sup>10,14,15</sup> confirming the absence of any glycosidic attachment at the 11-OH or 12-OH groups. Similar effects were noted for the other megalomicins and for the 9-dihydroderivatives (61) and (62) (Table 6). Comparison of the <sup>13</sup>C n.m.r. parameters for the methyl L-megosaminides (37), (38), (43), and (44) (Table 1) with those of the megalomicins (Table 6) supported the fact that this sugar occurred in the pyranoside form in the antibiotics, confirming previous mass-spectral deductions.<sup>6</sup> The measurement of the anomeric <sup>13</sup>C-<sup>1</sup>H coupling constants for megalomicin B (2) confirmed the equatorial glycosidic linkage <sup>16,17,27,28</sup> ( $\alpha$ -L-<sup>4</sup>C<sub>1</sub>) of the L-megosamine unit [ $J(^{13}\text{C}-^1\text{H})$  158 Hz], a conclusion that had previously been reached by the application of Klyne's rule of optical rotations.<sup>4,5</sup> The corresponding values for C-1 of  $\beta$ -D-desosamine [<sup>4</sup>C<sub>1</sub>,  $J(^{13}\text{C}-^1\text{H})$  158 Hz] and for C-1''' of  $\alpha$ -L-mycarose [<sup>1</sup>C<sub>4</sub>,  $J(^{13}\text{C}-^1\text{H})$  166 Hz] in megalomicin B (2) were in agreement with the

assigned anomeric linkages of these sugars to the aglycone. The deshielding of the 9-ketone carbon in erythromycin A (58) ( $\delta_{\text{C}}$  221.3) has been attributed specifically to hydrogen bonding between the 6-OH group and the ketone.<sup>10</sup> In the megalomicins where the 6-OH group is glycosylated the 9-ketone carbons still exhibit similar chemical-shift values (Table 6), clearly indicating that the 9-ketones are still hydrogen-bonded. The X-ray data revealed that this hydrogen bond was formed from the 11-OH group in megalomicin A, as the interatomic distance between the oxygen atoms of the 11-OH and 9-oxo-groups was found to be 2.93 Å.

It has been suggested<sup>10</sup> that erythromycin derivatives lacking the 3-O-glycosyl moiety exhibit hydrogen bonding between the 3-OH group and the anomeric oxygen of the 5-O-glycoside resulting in deshielding of C-5. It is evident from Table 6 that C-5 in megalosamine (59) ( $\delta_{\text{C}}$  89.0) is deshielded relative to megalomicin A (1) ( $\delta_{\text{C}}$  82.9), while in (9S)-9-dihydromegalosamine (62) ( $\delta_{\text{C}}$  85.9) the deshielding is less pronounced. On the

other hand (61) ( $\delta_C$  93.6) exhibited a marked deshielding for C-5 while (9S)-2',4'',9,11-tetra-*O*-benzoyl-9-dihydro-megalalosamine (63) ( $\delta_C$  83.0) and 2',4''-di-*O*-benzoyl-megalalosamine (64) ( $\delta_C$  82.5) exhibited no change at all and 3-*O*-acetyl-2',4''-di-*O*-benzoylmegalalosamine (65) ( $\delta_C$  80.4) was shielded. If one now considers the anomeric carbon C-1' of desosamine it is apparent that in megalalosamine (59) ( $\delta_C$  106.1), (9S)-9-dihydro-megalalosamine (62) ( $\delta_C$  105.1), and (61) ( $\delta_C$  106.2) it is deshielded relative to megalomicin A (1) ( $\delta_C$  104.5). On the other hand C-1' in the acyl derivatives (63) ( $\delta_C$  100.7), (64) ( $\delta_C$  99.8) and (65) ( $\delta_C$  100.1) is shielded relative to megalomicin A (1). These chemical shifts cannot be interpreted solely in terms of hydrogen bonding between the 3-OH group and the 5-glycoside oxygen. In order to better visualize the effect of certain transformations on the chemical shifts of C-3, C-5, C-6, C-1', and C-1'' the  $\Delta\delta_C$  values for selected megalalosamine derivatives were calculated and are given in Table 7. Removal of the mycarose moiety [(1)→(59)] does produce deshielding of

TABLE 7  
 $\Delta\delta_C$  Values for the megalalosamines

Carbon	$\Delta\delta_C$				
	(1)→(59)	(59)→(64)	(64)→(65)	(59)→(62)	(62)→(63)
C-3	-7.6	-1.6	+2.1	0	-0.1
C-5	+6.1	-6.5	-2.1	-3.1	-2.9
C-6	-0.1	+0.4	0	+2.7	-0.6
C-1'	+1.6	-6.3	+0.3	-1.0	-4.4
C-1''	+0.4	+1.2	-0.2	+0.4	+0.4

C-5 and to a lesser extent of C-1'. However, benzoylation of the 2'-OH and 4''-OH groups [(59)→(64)] shields both C-5 and C-1' and deshields C-1'' thus accounting for the observed chemical shifts in (64). Acetylation of the 3-OH group [(64)→(65)] results in shielding of C-5 by only 2.1 p.p.m. The chemical shifts for the 9-dihydro-derivatives (62) and (63) may be rationalized in terms of the component  $\Delta\delta_C$  values from Table 7. It appears that hydrogen-bonding effects and anisotropic effects of the acyl groups are insufficient to explain the observed chemical shifts. Changes in the conformations about the glycosidic bonds and perhaps even some conformational reorganization of the aglycone in the C-1—C-6 region<sup>29</sup> would seem to need to be invoked to explain the observed chemical shifts for the carbons in question.

In order to determine the effects of acylation of the glycosyl moieties upon the chemical shifts of C-3, C-5, C-6, C-1', and C-1'' and C-1''' in the megalomicins, the  $\Delta\delta_C$  values for selected derivatives were calculated and

are given in Table 8. Thus acylation of the 4'''-OH group [(1)→(2)] resulted in shielding of C-3 and C-1'. Acylation of the 2'-OH and 4''-OH groups [(2)→(60)] produced shielding of C-5, and C-1' and deshielding of C-1''. Acylation of 3'''-OH and 4'''-OH groups [(1)→(3) and (1)→(4)] resulted in shielding of C-3, C-1''' and C-1' only. By comparing (2)→(3) and (2)→(4) it is evident that acylation of the 3'''-OH group alone would produce no significant change in the chemical shifts. It is difficult to rationalize these changes without invoking some change in conformation about the glycosidic bonds.

The failure of the secondary 11-OH group in megalomicin A (1) to undergo acylation under forcing conditions was originally interpreted as evidence for the location of the L-megosamine at that position.<sup>4,5</sup> The only by-product formed during the acylation reaction was postulated from the absence of the ketone absorption in the i.r. to be a hemiacetal acetate.<sup>5</sup> This conclusion was verified by running the <sup>13</sup>C n.m.r. spectrum of 4''',9-di-*O*-acetyl-2',3''',4'''-tri-*O*-propionylmegalomicin A 9,12-hemiacetal (68), the by-product formed by acetylation of 2',4'',4'''-tri-*O*-propionylmegalomicin A under vigorous conditions. The hemiacetal (68) showed no carbonyl absorption in the i.r. and the <sup>13</sup>C n.m.r. spectrum (Table 6) confirmed the absence of the 9-carbonyl carbon. A signal at  $\delta_C$  108.5 was consistent with an acetylated hemiacetal at C-9. The deshielding of C-12 and the chemical shifts of the aglycone carbons, indicated that the hemiacetal was formed from the 12-OH and the 9-ketone in (68). Similar chemical shifts have been reported previously for anhydro-erythromycin A,<sup>10</sup> which has a similar partial structure in the C-10—C-12 region. Deshielding of the 12-Me group to  $\delta_C$  25.8 was also consistent with the formation of a 9,12-hemiacetal. It is also of interest to note that in the hemiacetal (68), no acetylation of the secondary 11-OH group occurred. It is apparent from the X-ray results and from space-filling models that the 11-OH group is extremely hindered in the megalomicins due to the presence of the L-megosamine unit, and that it would not be readily acylated. The only examples of acylation of the 11-OH group were in the 9-dihydro-derivatives where propionylation under forcing conditions afforded the pentapropionate (66),<sup>30</sup> while benzoylation under similar conditions gave the tetrabenzoate (63) having the 3-OH group free. The acylation of the 11-OH group must be occurring by *trans*-acylation from the 9-OH group, as no acylation at the 11-OH group was observed

TABLE 8  
 $\Delta\delta_C$  Values for the megalomicins

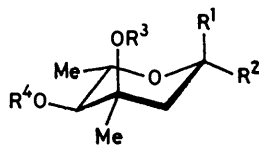
Carbon	$\Delta\delta_C$						
	(1)→(2)	(1)→(60)	(2)→(60)	(1)→(3)	(2)→(3)	(1)→(4)	(2)→(4)
C-3	-2.9	-3.0	-0.1	-3.3	-0.4	-3.3	-0.4
C-5	+0.4	-0.5	-0.9	+0.1	-0.3	+0.1	-0.3
C-6	-0.1	+0.3	+0.4	-0.3	-0.2	-0.2	-0.1
C-1'	-1.4	-4.3	-2.9	-1.9	-0.5	-2.0	-0.6
C-1''	-0.1	+1.0	+1.1	0	+0.1	-0.1	0
C-1'''	-0.6	-0.2	+0.4	-1.0	-0.4	-1.0	-0.4



under similar forcing conditions with the 9-oxo-derivatives. The shielding of the 12-Me group in (63) to  $\delta_{\text{H}}$  0.53 can only be explained by assuming that the aromatic ring lies over the 12-Me group and approximately parallel to the plane of the aglycone ring. Models show that the normal conformation having the benzoate carbonyl group aligned with H-11 would not be expected due to steric interaction with the L-megosamine unit. The absence of any signal due to H-3 at low field in (63) as well as the failure of megalalosamine (59) to undergo benzoylation at C-3 under similar conditions indicated that the 3-OH group was free in (63).

The observed variations which occurred in some cases between the carbon chemical shifts in the methyl glycosides relative to the corresponding shifts in the antibiotics are most probably due to steric interactions with either the aglycone or a neighbouring glycoside. Reduction of the 9-oxo-group in megalalosamine (59) to give the 9-dihydro-derivative (62) resulted in shielding of C-7, C-8, and C-10, while C-6 and C-11 were deshielded. Similar shieldings have been reported upon reduction of the oxo-group in erythronolide B.<sup>10</sup>

The only significant mass-spectral fragment affected by the revised location of L-megosamine is the ion hh.<sup>6</sup> However, if one invokes initial losses of the D-desosamine and L-mycarose units with cleavage of the C-10—C-11 and lactone bonds as shown in the Scheme, a reasonable alternative structure may be written for the ion hh



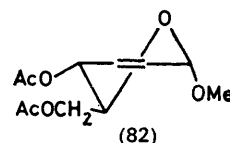
- (53)  $R^1 = \text{OMe}, R^2 = R^3 = R^4 = \text{H}$   
 (54)  $R^1 = \text{OMe}, R^2 = R^3 = \text{H}, R^4 = \text{Ac}$   
 (55)  $R^1 = R^3 = \text{H}, R^2 = \text{OMe}, R^4 = \text{Ac}$   
 (56)  $R^1 = \text{OMe}, R^2 = \text{H}, R^3 = \text{Ac}, R^4 = \text{COEt}$   
 (57)  $R^1 = \text{H}, R^2 = \text{OMe}, R^3 = \text{Ac}, R^4 = \text{COEt}$

which has the correct composition.<sup>6</sup> This mechanism would suggest that L-megosamine is retained in ion hh.<sup>6</sup> The alternative structure for hh<sup>1</sup> is not compatible with the 2'- and 4''-mono-acyl derivatives of the megalomycins<sup>6</sup> and should therefore be discarded.

The absolute stereochemistry at C-5 of L-megosamine was originally deduced from the sign of the c.d. extremum of a ca. 1:1 mixture of  $\alpha$ - and  $\beta$ -anomers of what was considered to be the ketone (69). The 5-Me group was predicted to govern the sign of the c.d. as each of the 1-OMe groups ( $\alpha$ - and  $\beta$ -anomers) would lie in opposite octants and would tend to cancel one another, thus leading to a negative extremum for a D-sugar, based on numerous 2-methylcyclohexanone and 2,4-dimethylcyclohexanone examples in the literature.<sup>31</sup> The effect of the pyranoside ring oxygen was unknown. The observed value of  $[\theta]_{298}^{298}$  ( $-3.531$ ) appeared to agree with a D-configuration at C-5.<sup>8,9</sup> This was obviously incorrect based on the X-ray study and in order to determine why this was so, a series of model ketones had to be synthesized.

3,4,6-Tri-*O*-acetyl-D-glucal was converted into the pseudo-glucal (82)<sup>32</sup> and the latter was subjected to catalytic reduction and ammonolysis to give methyl 2,3-dideoxy- $\alpha$ -D-erythro-hexopyranoside (70).<sup>33</sup> The benzylidene derivative (71)<sup>34</sup> was prepared<sup>26</sup> and then reacted with *N*-bromosuccinimide to give methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy- $\alpha$ -D-erythro-hexopyranoside (72).<sup>35,36</sup> The bromide (72) was heated under reflux with lithium aluminium hydride in tetrahydrofuran to give methyl  $\alpha$ -D-amicetoside (73).<sup>36,37</sup> Oxidation of the alcohol (73) with ruthenium tetroxide afforded methyl  $\alpha$ -D-cineruloside (69).

Reduction of the pseudo-glucal (82)<sup>32</sup> with lithium aluminium hydride gave 3-deoxy-D-glucal (83)<sup>38</sup> which



was catalytically hydrogenated to give 1,5-anhydro-2,3-dideoxy-D-erythro-hexitol (74).<sup>39,40</sup> The latter was converted into the benzylidene derivative (75)<sup>40</sup> which was reacted with *N*-bromosuccinimide to afford 1,5-anhydro-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-D-erythro-hexitol (76). Lithium aluminium hydride reduction of (76) gave 1,5-anhydro-2,3,6-trideoxy-D-erythro-hexitol (77) which on oxidation with ruthenium tetroxide afforded 1,5-anhydro-2,3,6-trideoxy-D-glycero-hexitol-4-ulose (78).

1,2,3,4-Tetra-*O*-acetyl- $\beta$ -D-xylopyranose (84)<sup>41</sup> was treated with titanium tetrabromide to give the pyranosyl bromide which on reduction with a zinc-copper couple in aqueous acetic acid gave 3,4-di-*O*-acetyl-D-xylal (85).<sup>42,43</sup> Treatment of the xylal (85) with methanol and boron trifluoride-ether (1/1) gave methyl 4-*O*-acetyl-2,3-dideoxy- $\alpha$ -D-glycero-pent-2-enopyranoside (86) which was directly hydrogenated and saponified to give methyl 2,3-dideoxy- $\alpha$ -D-glycero-pentopyranoside (79). Oxidation of the latter with ruthenium tetroxide afforded (2*S*)-2-methoxytetrahydropyran-5-ulose (80).

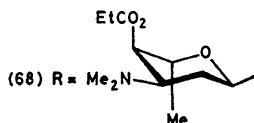
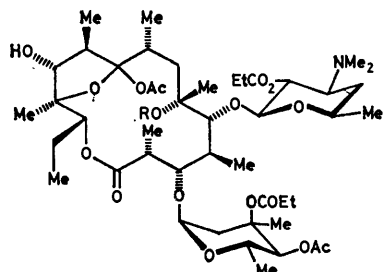
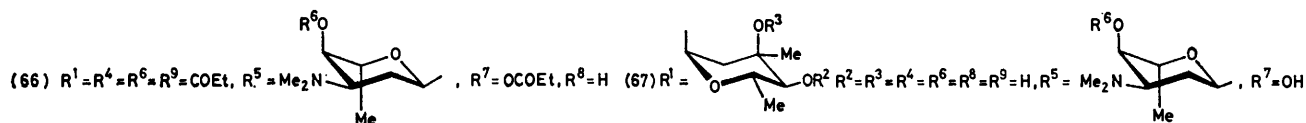
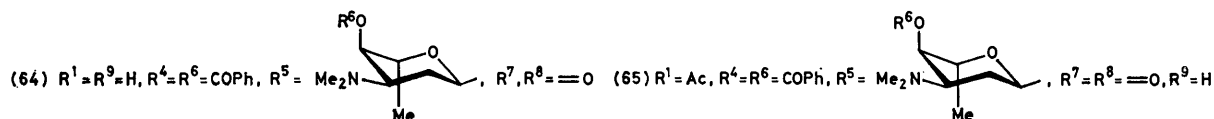
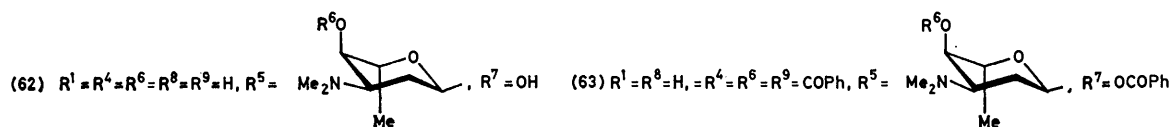
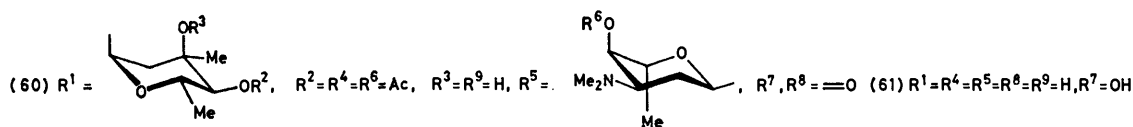
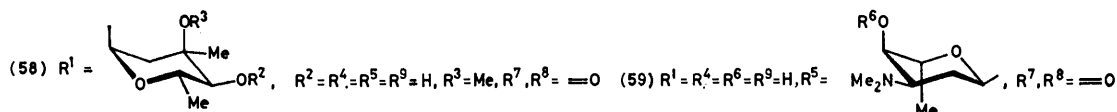
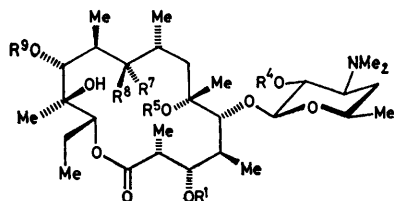
In order to verify that no epimerizations were occurring during the oxidations with ruthenium tetroxide, two ketones were prepared in the L-series. 3,4-Di-*O*-acetyl-L-rhamnol (87)<sup>44,45</sup> was prepared by a modification of the literature procedure. Reaction of (87) with methanol and boron trifluoride-ether (1/1) gave methyl 4-*O*-acetyl-2,3,6-trideoxy- $\alpha$ -L-erythro-hex-2-enopyranoside (88).<sup>46</sup> Catalytic hydrogenation of (88) followed by ammonolysis afforded methyl L-amicetoside (89).<sup>46-49</sup> Oxidation of the latter with ruthenium tetroxide gave methyl  $\alpha$ -L-cineruloside (90).<sup>48,50</sup>

Reduction of (88) with lithium aluminium hydride afforded 3-deoxy-L-rhamnol (94). Catalytic hydrogenation of (94) gave 1,5-anhydro-2,3,6-trideoxy-L-erythro-hexitol (91) which was oxidized with ruthenium tetroxide to give 1,5-anhydro-2,3,6-trideoxy-L-glycero-hexitol-4-ulose (92).

The <sup>1</sup>H and <sup>13</sup>C n.m.r. parameters (Table 9) for the

ketones and the precursor alcohols indicate that these model sugars exist in the expected  ${}^4C_1$  (D-series) and  ${}^1C_4$  (L-series) conformations. It was also apparent from the

methanol and the data are given in Table 10, together with the calculations of the contributions arising from the various component portions of the molecule. It is

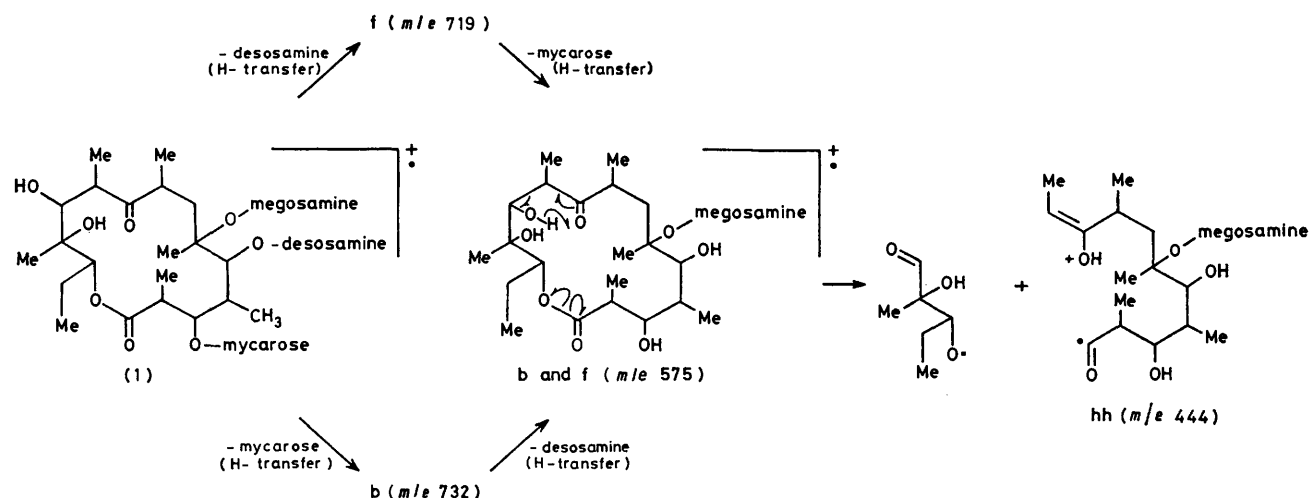


specific rotations that no epimerization was occurring during the ruthenium tetroxide oxidation step. The c.d. spectra of the model ketones were recorded in

evident that the methyl group makes the greatest contribution to the c.d. extremum, as was originally predicted.<sup>8,9</sup> In the  $\alpha$ -glycosides the anomeric OMe

group makes a lesser contribution, but is of the same sign as that of the methyl group, while the ring oxygen makes a contribution of the opposite sign. It is apparent

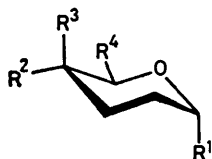
$\alpha$ - and  $\beta$ -anomers of the ketone (90)<sup>8,9</sup> is consistent with the fact that the anomeric OMe group in the  $\beta$ -anomer would lie in a positive octant (Figure 3). Presumably



from Table 10 that these ketones do not obey the normal Octant rule, but instead constitute further examples of a small group of ketones that exhibit anti-octant behaviour.<sup>51</sup> The c.d. spectra of these ketones are in full agreement with the Anti-octant rule (Figure 2) which

the ring oxygen is responsible for the anomalous c.d. behaviour of these ketones.

With hindsight it is also interesting to note the excel-



- (69)  $R^1 = \text{OMe}, R^2, R^3 = =\text{O}, R^4 = \text{Me}$   
 (70)  $R^1 = \text{OMe}, R^2 = \text{OH}, R^3 = \text{H}, R^4 = \text{CH}_2\text{OH}$   
 (71)  $R^1 = \text{OMe}, R^2, R^4 = \text{PhCH} \begin{matrix} \text{OCH}_2^- \\ \text{O}^- \end{matrix}, R^3 = \text{H}$   
 (72)  $R^1 = \text{OMe}, R^2 = \text{OCOPh}, R^3 = \text{H}, R^4 = \text{CH}_2\text{Br}$   
 (73)  $R^1 = \text{OMe}, R^2 = \text{OH}, R^3 = \text{H}, R^4 = \text{Me}$   
 (74)  $R^1 = R^3 = \text{H}, R^2 = \text{OH}, R^4 = \text{CH}_2\text{OH}$   
 (75)  $R^1 = R^3 = \text{H}, R^2, R^4 = \text{PhCH} \begin{matrix} \text{OCH}_2^- \\ \text{O}^- \end{matrix}$   
 (76)  $R^1 = R^3 = \text{H}, R^2 = \text{OCOPh}, R^4 = \text{CH}_2\text{Br}$   
 (77)  $R^1 = R^3 = \text{H}, R^2 = \text{OH}, R^4 = \text{Me}$   
 (78)  $R^1 = \text{H}, R^2, R^3 = =\text{O}, R^4 = \text{Me}$   
 (79)  $R^1 = \text{OMe}, R^2 = \text{OH}, R^3 = R^4 = \text{H}$   
 (80)  $R^1 = \text{OMe}, R^2, R^3 = =\text{O}, R^4 = \text{H}$   
 (81)  $R^1 = R^2 = R^3 = \text{H}, R^4 = \text{Me}$

would not have been predicted *a priori* in 1969 based on what was known at that time. The lower amplitude observed for the c.d. extremum of the 1:1 mixture of

the ring oxygen is responsible for the anomalous c.d. behaviour of these ketones.

With hindsight it is also interesting to note the excel-

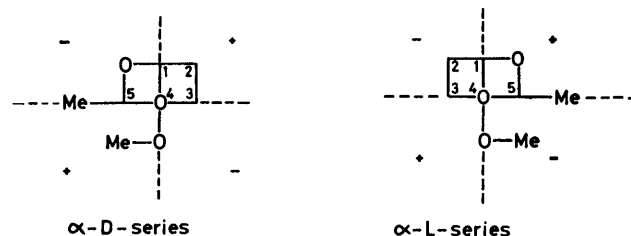


FIGURE 2 Anti-octant diagrams

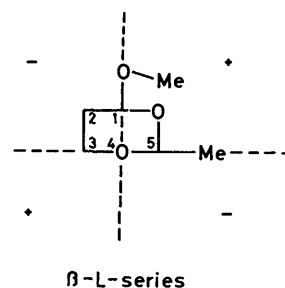


FIGURE 3 Anti-octant diagram

would not have been predicted *a priori* in 1969 based on what was known at that time. The lower amplitude observed for the c.d. extremum of the 1:1 mixture of

lent correlation between the data reported<sup>48</sup> for methyl  $\alpha$ -L-amicetoside (89) and methyl  $\beta$ -L-amicetoside (93) with the data that we reported<sup>8,9</sup> for a 1:1 mixture of

TABLE 9

Carbon-13 chemical shifts (p.p.m. downfield from  $\text{SiMe}_4$  in  $\text{CDCl}_3$ )

Carbon	(73)	(90)	$\Delta\delta_c(73) \rightarrow (90)$	(77)	(92)	$\Delta\delta_c(77) \rightarrow (92)$	(81) *	(79)	(80)	$\Delta\delta_c(79) \rightarrow (80)$	(98)	(102)
C-1	97.4	97.9	+0.5	67.5	65.9	-1.6	68.5	99.1	97.4	-1.7	98.5	100.7
C-2	27.6	29.1	+1.5	25.8	26.6	+0.8	26.0	25.5	28.2	+2.7	37.8	39.1
C-3	29.6	33.6	+4.0	32.8	37.5	+4.7	23.7	26.0	33.7	+7.7	69.2	71.8
C-4	72.0	210.2		72.1	208.8		33.8	65.3	208.4		78.1	77.4
C-5	69.4	70.9	+1.5	78.7	79.7	+1.0	73.9	65.3	67.1	+1.8	67.6	71.5
C-6	18.0	14.9	-3.1	18.3	15.2	-3.1	22.2				17.7	17.8
l-OMe	54.4	55.2	+0.8					55.2	53.3	+0.1	54.6	56.6

\* Purchased from Aldrich and run as a model compound.

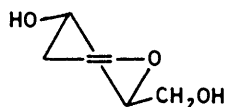
TABLE 10  
Circular dichroism of model ketones (in CH<sub>3</sub>OH)

Compound	D-Series λ/nm	[θ]	Compound	L-Series λ/nm	[θ]
(69)	298	+5 190	(90)	298	-5 060
(78)	301	+1 890	(92)	301	-2 390
(80)	295	-542			
Ring-O + OMe	+ Me =	+5 190	Ring O + Me + OMe	=	-5 060
Ring-O	+ Me =	+1 890	Ring-O	+ Me =	-2 390
	OMe =	+3 300		OMe =	-2 670
Ring-O + OMe	+ Me =	+5 190	Ring-O + OMe + Me	=	-5 060
Ring-O + OMe	=	-542	Ring-O + OMe	=	+542 *
	Me =	+5 732		Me =	-5 602
Ring-O + OMe	=	-542	Ring-O + OMe	=	+542 *
	OMe =	+3 300		OMe =	-2 670
Ring-O	=	-3 842	Ring-O	=	+3 212

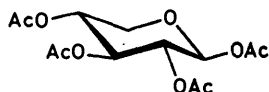
\* Assumed to be equal and opposite to the D-series.

anomers that are now recognized to be the same compounds.

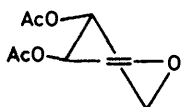
Final chemical proof of the structure of L-megosamine was obtained by synthesis of methyl α-L-megosaminide (37) and the β-anomer (38) as follows. Methoxy-



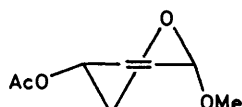
(83)



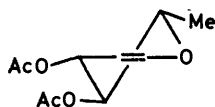
(84)



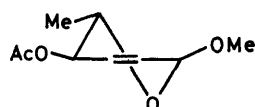
(85)



(86)



(87)



(88)

mercuriation<sup>52</sup> of 3,4-di-O-acetyl-L-rhamnal (87)<sup>44,45</sup> gave a mixture of anomers [(95) and (96)] from which the β-anomer (96) crystallized.<sup>52</sup> The mother liquors comprised the α-anomer (95) as a gum. Reduction of (95) with sodium borohydride gave methyl 3,4-di-O-acetyl-2,6-dideoxy-α-L-arabino-hexopyranoside (97)<sup>52</sup> which was saponified to give the alcohol (98).<sup>52-55</sup> Selective reaction with *p*-toluenesulphonyl chloride afforded the 3-*p*-toluenesulphonate (99)<sup>56</sup> which on treatment with sodium azide gave a moderate yield of the azide (100).<sup>54,57</sup> Reductive formylation of (100) gave methyl 2,3,6-trideoxy-3-dimethylamino-α-L-ribo-hexopyranoside (methyl L-megosaminide) (37) which was identical with the natural material. In a similar manner the β-anomer (101)<sup>52</sup> prepared by sodium borohydride reduction of (96) was converted into alcohol (102)<sup>52,54</sup> which was then selectively reacted with *p*-toluenesulphonyl

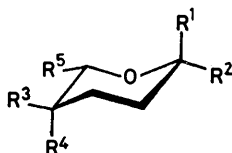
chloride to give (103).<sup>54</sup> The latter was converted into the azide (104)<sup>54,57</sup> which on reductive formylation gave methyl β-L-megosaminide (38) which was identical with the natural sample. The <sup>1</sup>H and <sup>13</sup>C n.m.r. parameters (Table 1) for the azides (100) and (104) confirmed the fact that these molecules exist in the <sup>1</sup>C<sub>4</sub> conformation. The ring flips to the <sup>4</sup>C<sub>1</sub> conformation upon introduction of the more bulky dimethylamino-group. The <sup>13</sup>C n.m.r. parameters of (98) and (102) are given in Table 9.

Methyl α-D-megosaminide (41) and the β-anomer (42) were also synthesized as follows. The known methyl 4,6-O-benzylidene-2-deoxy-3-O-methanesulphonyl-α-D-arabino-hexopyranoside (28)<sup>58</sup> was treated with *N*-bromosuccinimide to give the bromo-sugar (29), which on catalytic reduction afforded the 6-deoxy-sugar (30). The latter was converted to the azide (31), which on reductive formylation gave methyl α-D-megosaminide (41). The <sup>13</sup>C and <sup>1</sup>H n.m.r. parameters of (41) were in excellent agreement with those of (37). The azide (31) was equilibrated with methanolic hydrogen chloride to give a mixture of the α- (31) and β-anomers (33) (3 : 7) which were chromatographically inseparable. The latter was converted into the anomeric mixture of azides (32) and (34) (3 : 7) which again could not be separated. Reductive formylation of the latter afforded an inseparable mixture of methyl α-D-megosaminide (41) and methyl β-D-megosaminide (42) (3 : 7). The <sup>13</sup>C and <sup>1</sup>H n.m.r. parameters of (42) recorded on the mixture were in agreement with those of (38). Similar ring inversions from the <sup>4</sup>C<sub>1</sub> to the <sup>1</sup>C<sub>4</sub> conformations were observed in the D-series, as discussed for the L-series, upon introduction of the bulky dimethylamino-group.

Reductive formylation of methyl 3-azido-2,3,6-trideoxy-α-D-arabino-hexopyranoside (18) afforded methyl α-D-angolosaminide (35),<sup>59</sup> while similar treatment of the β-azide (24) gave methyl β-D-angolosaminide (36).<sup>59</sup> D-Angolosamine is a sugar component of the macrolide antibiotic angolamycin.<sup>60,61</sup> The <sup>13</sup>C n.m.r. parameters for the novel azido- and dimethylamino-sugars are given in Table 1.

It was evident from the X-ray study on megalomicin A that in the crystal state the observed rotamers about the C-3'-N and C-3''-N bonds of the dimethylamino-groups are different in desosamine and megosamine. It

was of interest, therefore, to determine whether such rotamers also occurred in solution, as they would be



- (89)  $R^1 = \text{OMe}, R^2 = R^4 = \text{H}, R^3 = \text{OH}, R^5 = \text{Me}$   
 (90)  $R^1 = \text{OMe}, R^2 = \text{H}, R^3, R^4 = =\text{O}, R^5 = \text{Me}$   
 (91)  $R^1 = R^2 = R^4 = \text{H}, R^3 = \text{OH}, R^5 = \text{Me}$   
 (92)  $R^1 = R^2 = \text{H}, R^3, R^4 = =\text{O}, R^5 = \text{Me}$   
 (93)  $R^1 = R^4 = \text{H}, R^2 = \text{OMe}, R^3 = \text{OH}, R^5 = \text{Me}$

predicted to cause markedly different shielding of the  $\gamma$ -carbons in the  $^{13}\text{C}$  n.m.r. spectra of these compounds. The rotamer preference would be expected to be affected by the presence of substituents on these  $\gamma$ -carbons, as

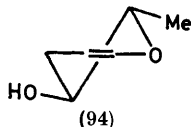
(111). Each substituent would be expected to introduce a single 1,3-interaction between the methyl group of the methoxy-,<sup>64,65</sup> or the  $\beta$ -nitrogen of the azide<sup>66</sup> and one of the hydrogen atoms at either C-2, or C-6 as illustrated by rotamer (a) (Figure 4), resulting in the observed shielding. The removal of the *gauche* interaction between the hydrogen of the hydroxy-group and C-2, or C-6 would also be expected to contribute to the observed shielding in the methoxy- and azido-derivatives.<sup>64</sup> The introduction of the *N*-methyl group in (114) removes one of the *gauche* hydrogen interactions and introduces a single 1,3-interaction which results in shielding of C-2 and C-6 ( $-3.9$ ) relative to the amine (112) as illustrated by rotamer (b) (Figure 4). The introduction of a dimethylamino-group in (115) removes two *gauche* hydrogen interactions and at the same time

TABLE 11  
 $\gamma$ -Effects for OMe,  $\text{N}_3$ , NHMe and  $\text{NMe}_2$  substituents in cyclohexanes and hexopyranosides

Carbon	$\delta_c$			$\Delta\delta_c$				
	(105) <sup>62</sup> [ $\text{NH}_2$ ]	(21) [ $\text{N}_3$ ]	(7) [ $\text{NMe}_2$ ]	(105) $\rightarrow$ (21)	(21) $\rightarrow$ (7)	(105) $\rightarrow$ (7)	(105) $\rightarrow$ (7)	
$\alpha$ -Anomer								
C-2	32.3	28.5	28.5	-3.8	0	-3.8	-3.8	
C-4	70.5	69.9	66.1	-0.6	-3.8	-4.4	-4.4	
$\beta$ -Anomer		(27) [ $\text{N}_3$ ]	(8) [ $\text{NMe}_2$ ]		(27) $\rightarrow$ (8)			
C-2		30.3	30.7		+0.4			
C-4		69.7	65.8		-3.9			
$\alpha$ -Anomer	(98) [OH]	(106) <sup>15</sup> [OMe]	(18) [ $\text{N}_3$ ]	(35) [ $\text{NMe}_2$ ]	(98) $\rightarrow$ (106)	(98) $\rightarrow$ (18)	(18) $\rightarrow$ (35)	(98) $\rightarrow$ (35)
C-2	37.8	34.0	35.0	25.7	-3.8	-2.8	-9.3	-12.1
C-4	78.1	76.1	76.2	71.7	-2.0	-1.9	-4.5	-6.4
$\beta$ -Anomer	(102) [OH]		(24) [ $\text{N}_3$ ]	(36) [ $\text{NMe}_2$ ]	(102) $\rightarrow$ (24)	(24) $\rightarrow$ (36)	(102) $\rightarrow$ (36)	
C-2	39.1		35.9	27.1	-3.2	-8.8	-12.0	
C-4	77.4		75.6	71.3	-1.8	-4.3	-6.1	
$\alpha$ -Anomer		(107) <sup>11</sup> [OMe]		(109) <sup>14</sup> [ $\text{NMe}_2$ ]			(107) $\rightarrow$ (109)	
C-2		73.0		68.7			-4.3	
C-4		37.4		29.3			-8.1	
$\beta$ -Anomer		(108) <sup>11</sup> [OMe]		(110) <sup>14</sup> [ $\text{NMe}_2$ ]			(108) $\rightarrow$ (110)	
C-2		74.7		69.9			-4.8	
C-4		37.4		28.8			-8.6	
$\text{C}_2, \text{C}_6$	(111) <sup>63</sup> [OH]	(116) <sup>63</sup> [OMe]	(113)* [ $\text{N}_3$ ]		(111) $\rightarrow$ (116)	(111) $\rightarrow$ (113)	(112) $\rightarrow$ (113)	(111) $\rightarrow$ (112)
	35.7	32.2	32.3		-3.5	-3.4	-5.1	+1.7
$\text{C}_2, \text{C}_6$	(112) <sup>63</sup> [ $\text{NH}_2$ ]	(114)* [NHMe]	(115)* [ $\text{NMe}_2$ ]		(112) $\rightarrow$ (114)	(112) $\rightarrow$ (115)	(114) $\rightarrow$ (115)	(113) $\rightarrow$ (115)
	37.4	33.5	29.0		-3.9	-8.4	-4.5	-3.3

\* Unpublished observations (G. Lukacs).

well as by the stereochemistry of such substituents. Knowledge of these  $\gamma$ -effects would be valuable in assigning structures to novel methylamino- and dimethylamino-sugars which occur in many antibiotics. From the  $^{13}\text{C}$  n.m.r. parameters of the novel sugars synthesized during this study and from data available in the literature,<sup>62,63</sup> it was possible to evaluate the  $\gamma$ -effects for OMe,  $\text{N}_3$ , and  $\text{NMe}_2$  groups in selected hexopyranosides in relation to the corresponding effects in *trans*-4-*t*-butylcyclohexane derivatives (Table 11).



In the cyclohexane series, which are symmetrical and which have no steric constraints imposed on the 1-substituent by neighbouring substituents on C-2 or C-6, it is evident from the  $\Delta\delta_c$  values that both the methoxy ( $-3.5$ ) and azido ( $-3.4$ ) groups in (116) and (113) respectively, shield C-2 and C-6 relative to the alcohol

introduces two 1,3-interactions which result in greater shielding of C-2 and C-6 ( $-8.4$ ) relative to the amine (112) as shown in rotamer (c) (Figure 4).

In the case of the hexopyranosides, additional steric constraints have to be considered which are governed by the presence of substituents on the neighbouring carbons, as well as by the stereochemistry of these substituents. It is known for cyclitols<sup>67</sup> and sugars<sup>68</sup> that methylation of an equatorial alcohol, which is flanked by carbons bearing an equatorial and an axial hydroxy-group respectively, will only produce a pronounced up-field shift of the carbon bearing the axial substituent. This observed  $\gamma$ -effect has been attributed to the 1,3-interaction between the methyl group of the methoxy- and the equatorial hydrogen on the carbon bearing the axial hydroxy-group, and has been utilized to explain the observed  $\gamma$ -shieldings in certain hexuloses.<sup>65</sup> In contrast to the above results the azido-sugar (21), which has an axial hydroxy-group at C-4 and a methylene-group at C-2 exhibits a markedly different shielding pattern, in which the shielding at C-2 ( $-3.8$ ) is far more pronounced than that at C-4 ( $-0.6$ ) relative to L-

daunosamine in daunomycin (105).<sup>62</sup> Steric considerations, and the existence of hydrogen bonding between the alcohol and the  $\alpha$ -nitrogen of the azide, appear to lead to a preference for rotamer (*d*) (Figure 4) about the C-3-N bond in solution. Evidence for the existence of intramolecular hydrogen bonding in these azido-sugars was obtained by i.r. dilution studies on the azide (104) in carbon tetrachloride solution. At high concentrations free hydroxy ( $3625\text{ cm}^{-1}$ ), weak intramolecular hydro-

would again apply as for the azide (21), resulting in the predominance of rotamer (*e*) (Figure 4) in solution. Unlike the azide (21) this would result in shielding of both C-2 and C-4 as was observed. Evidence for intramolecular hydrogen bonding in these dimethylamino-sugars was again obtained by i.r. dilution studies on methyl  $\alpha$ -L-megosaminide (38) which showed a strong intramolecular hydrogen-bonded hydroxy-absorption ( $3470\text{ cm}^{-1}$ ) at all dilutions in carbon tetrachloride.

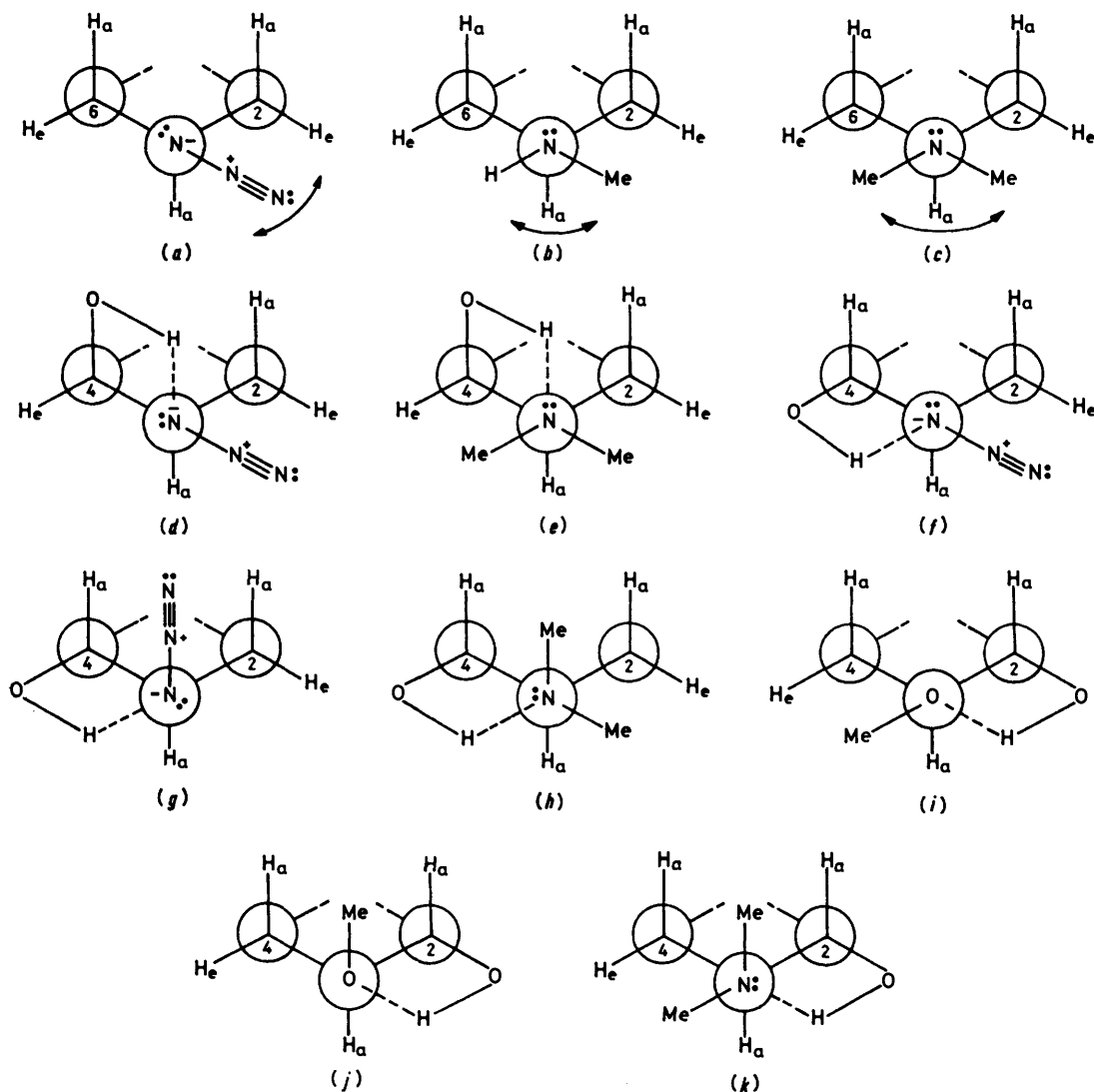


FIGURE 4

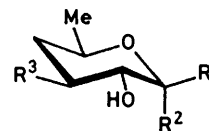
gen-bonded hydroxy ( $3575\text{ cm}^{-1}$ ), and strong intermolecular hydrogen-bonded hydroxy ( $3475\text{ cm}^{-1}$ ) absorptions were observed. On progressive dilution only the peak at  $3475\text{ cm}^{-1}$  disappeared. Hydrogen bonding has been noted previously in azido-alcohols.<sup>69</sup> Methyl  $\alpha$ -D-rhodosaminide (7) which also has an axial hydroxy-group at C-4 and a methylene group at C-2 exhibited shielding at both C-2 ( $-3.8$ ) and C-4 ( $-4.4$ ) relative to L-daunosamine in daunomycin (105).<sup>62</sup> Steric limitations and intramolecular hydrogen bonding

Similar results were obtained for the  $\beta$ -anomer (37) ( $3400\text{ cm}^{-1}$ ). The  $\beta$ -anomers (27) and (8) exhibited similar shieldings at C-2 and C-4 (Table 11).

Comparison of the  $^{13}\text{C}$  n.m.r. spectra of the sugar (98), which has an equatorial hydroxyl group at C-4 and a methylene group at C-2, with L-oleandrose in oleandomycin (106)<sup>15</sup> which has a 3-O-methyl substituent, reveals shielding of both C-2 ( $-3.8$ ) and C-4 ( $-2.0$ ) in (106). Comparison of (98) with the azide (18) also reveals shielding of both C-2 ( $-2.8$ ) and C-4 ( $-1.9$ ) in

(18). In the case of (106) and the azide (18) it would seem that an approximately equal distribution of rotamers (*f*) and (*g*) (Figure 4) exists, which would result in averaged shieldings being observed at C-2 and C-4. The presence of 1,3-interactions at C-2 in both (*f*) and (*g*) and at C-4 in (*g*) only would be expected to lead to greater shielding at C-2 than C-4 as was observed. In the case of methyl  $\alpha$ -D-angolosaminide (35), which has a 3-dimethylamino-group, both C-2 (-12.1) and C-4 (-6.4) are shielded relative to the corresponding alcohol (98). The larger shielding at C-2 relative to C-4 is due to the additional 1,3-interaction at C-2 resulting from the presence of the preferred rotamer (*h*) (Figure 4) in solution. Similar results were observed for the  $\beta$ -anomers (102), (24) and (36) (Table 11). Based on the above results, methyl  $\alpha$ -D-chalcoside (107)<sup>11</sup> would be expected to exist with an almost equal distribution of rotamers (*i*) and (*j*) (Figure 4) about the C-3-O bond. Methyl  $\alpha$ -D-desosaminide (109)<sup>14</sup> would be predicted to adopt rotamer (*k*) (Figure 4) in solution which would result in greater shielding at C-4 than C-2 in this case. Although base-line data for the corresponding 3-hydroxy-compounds are not available here,

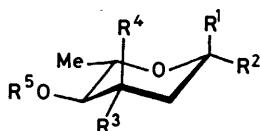
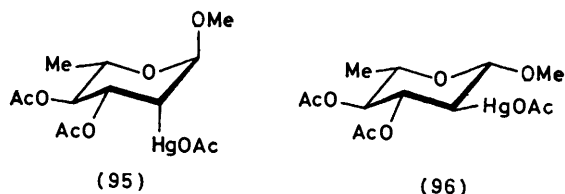
confirmed the presence of hydrogen bonding in the crystal state.<sup>70</sup> It is evident from the above studies that careful consideration has to be given to rotamer



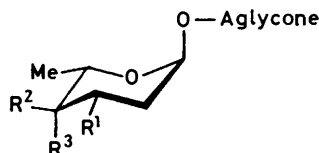
- (107)  $R^1 = H, R^2 = R^3 = OMe$   
 (108)  $R^1 = R^2 = OMe, R^3 = H$   
 (109)  $R^1 = H, R^2 = OMe, R^3 = NMe_2$   
 (110)  $R^1 = OMe, R^2 = H, R^3 = NMe_2$

populations before predicting the  $\gamma$ -effects for OMe,  $N_3$ , NHMe, and  $NMe_2$  groups in hexopyranosides, and further systematic work in this area appears desirable based on our limited observations on the examples described above.

C.d. studies carried out on a number of erythromycin derivatives<sup>71-73</sup> have contributed to the understanding of the conformations of these important macrolides. It was of interest to compare the c.d. parameters of erythromycin A (58) with those of selected megalomicin derivatives



- (97)  $R^1 = OMe, R^2 = R^4 = H, R^3 = OAc, R^5 = Ac$   
 (98)  $R^1 = OMe, R^2 = R^4 = R^5 = H, R^3 = OH$   
 (99)  $R^1 = OMe, R^2 = R^4 = R^5 = H, R^3 = OSO_2C_6H_4Me-p$   
 (100)  $R^1 = OMe, R^2 = R^3 = R^5 = H, R^4 = N_3$   
 (101)  $R^1 = R^4 = H, R^2 = OMe, R^3 = OAc, R^5 = Ac$   
 (102)  $R^1 = R^4 = R^5 = H, R^2 = OMe, R^3 = OH$   
 (103)  $R^1 = R^4 = R^5 = H, R^2 = OMe, R^3 = OSO_2C_6H_4Me-p$   
 (104)  $R^1 = R^3 = R^5 = H, R^2 = OMe, R^4 = N_3$



- (105)  $R^1 = NH_2, R^2 = H, R^3 = OH$   
 (106)  $R^1 = OMe, R^2 = OH, R^3 = H$

comparison of the  $\Delta\delta_C$  values in the anomers (107) and (109), and also the  $\beta$ -anomers (108) and (110) (Table 11), with those of oleandrose and rhodosamine, would support these conclusions. The X-ray study on megalomicin A revealed the fact that rotamer (*k*) is present in desosamine in the crystal state and also revealed a  $N \cdots O$  distance of 2.80 Å between the dimethylamino-group and the 2-hydroxy-group in desosamine, which



- (111)  $R = OH$   
 (112)  $R = NH_2$   
 (113)  $R = N_3$   
 (114)  $R = NHMe$   
 (115)  $R = NMe_2$   
 (116)  $R = OMe$

(Table 12). As anticipated, the megalomicins show two discrete negative c.d. extrema due to the lactone (209—215 nm) and ketone (288—289 nm) chromophores. The

TABLE 12

U.v. and c.d. data for the macrolides (in  $CF_3CH_2OH$ )

Compound	$\lambda/nm$	$\epsilon$	$\lambda/nm$	[ $\theta$ ]	$\Delta\epsilon$
(58)	278	137	210	-1 060	-0.32
			289	-5 940	-1.80
(1)			215	-2 030	-0.61
	280	53	288	-9 840	-2.98
(3)			209	-2 270	-0.69
	282	61	289	-9 940	-3.01
(4)			210	-2 460	-0.74
	283	54	289	-12 300	-3.74
(67)			210	-4 140	-1.26
(59)			210	-3 350	-1.02
	277	125	288	-9 840	-2.98
(62)			210	-3 430	-1.04
(61)			211	-6 980	-2.12

lactone chromophore would be expected to have negative chirality by the Beecham-Wolf<sup>74-78</sup> treatment, as the  $\beta$ -carbon to the lactone carbonyl (C-3 in the megalomicins) lies below the C-CO-O-C plane (Figure 5). Further refinements to assess the contributions of various portions of the molecule to the amplitude of the lactone extremum were derived by consideration of the Sznatzke sector diagram<sup>79</sup> (Figure 5). The X-ray results and models were used to place the sugars in the proper orientations so that their contributions to the c.d.

spectrum could be estimated. The megosamine would make a positive contribution while desosamine would make a negative contribution. The mycarosyl unit overlaps a nodal plane and it would appear to make an overall weak negative contribution. Using these contributions it would be predicted that the amplitude of the negative extremum would increase in going from megalalosamine (59) to megalomicin A (1). In the 9-dihydro-derivatives the amplitude of the lactone extremum would be expected to increase in going from (62) to (61) to (67). The increase in amplitude in going from megalomicin A (1) to megalomicin C<sub>1</sub> (3) and megalomicin C<sub>2</sub> (4) would also seem reasonable based on these assumptions. On the other hand erythromycin A (58) would have been expected to have a greater negative amplitude than was observed, based on the above assumptions.

Considering the 9-ketone chromophore of the megalomicins (Table 12), if one assumes that the normal Octant rule applies to these compounds, which seems reasonable in the light of data available from previous work on the erythromycins,<sup>71-73</sup> then one would predict a negative extremum at 290 nm as was indeed observed. The neighbouring  $\alpha$ -methyl groups at C-8 and C-10 would be expected to have a major effect on the c.d. extremum of the 9-ketone, and as the 10-Me group lies near the nodal plane, the 8-Me group would be expected to control the sign of the c.d. extremum as it lies well into a negative octant. Both mycarose and desosamine would be predicted to make positive contributions, while megosamine, which overlaps two octants, would have an overall negative contribution. The data in Table 12 appears to correlate reasonably well with the above

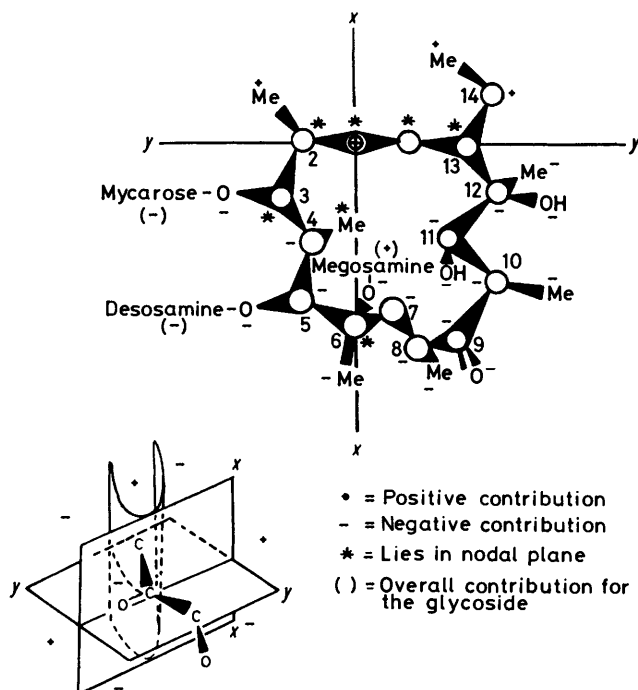
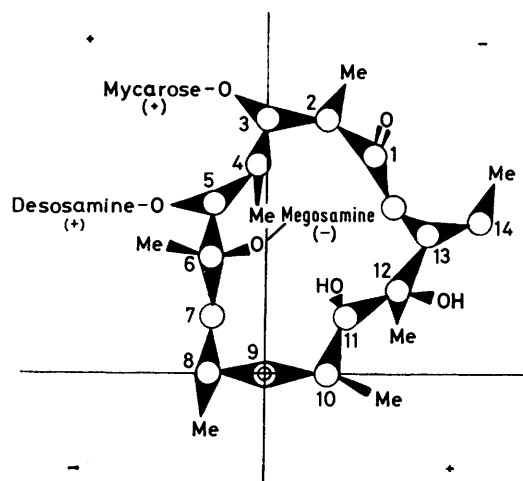


FIGURE 5 Sznatzke sector diagram for the lactone chromophore of megalomicin A (1)



( ) = Overall contribution for the glycoside

FIGURE 6 Normal octant rule for the ketone chromophore of megalomicin A (1)

conclusions, although megalalosamine (59) would have been predicted to have a slightly greater negative amplitude than was actually observed.

#### EXPERIMENTAL

Unless otherwise stated optical rotations were recorded at 26 °C (*c* 0.3%). I.r. spectra were recorded on Perkin-Elmer Infracord 137 or 221 spectrometers. C.d. spectra were run on a Cary 61 spectrometer. Mass spectra were recorded on a Varian MAT CH5 spectrometer. <sup>1</sup>H N.m.r. spectra were recorded at 60 MHz on a Varian T-60A instrument, at 100 MHz on a Varian XL-100-15 instrument, and at 79.5 MHz on a Varian CFT-20 instrument. <sup>13</sup>C N.m.r. spectra were obtained on a Varian XL-100-15 spectrometer in the Fourier-transform mode using a Varian 620L-100 16 K computer equipped with a 2.5 Megabyte disc system, or on a Bruker HX-90E spectrometer in the Fourier-transform mode. The *J*(<sup>13</sup>C-<sup>1</sup>H) values were measured on a CAMECA spectrometer operating at 62.87 MHz for <sup>13</sup>C. All chemical shift values are reported in p.p.m. downfield from tetramethylsilane.

*Methyl 4-O-Benzoyl-6-bromo-2,6-dideoxy-3-O-methanesulphonyl- $\alpha$ -D-ribo-hexopyranoside* (15).—A mixture of the known methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methanesulphonyl- $\alpha$ -D-ribo-hexopyranoside (14)<sup>18</sup> (6 g), barium carbonate (12 g), and *N*-bromosuccinimide (4 g) in anhydrous carbon tetrachloride (260 ml) was stirred under reflux for 2 h. The solution was filtered. The inorganic precipitate was washed with dichloromethane and the combined filtrate and washings were evaporated to dryness. Crystallization from ether-hexane afforded methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*O*-methanesulphonyl- $\alpha$ -D-ribo-hexopyranoside (15) (7.1 g, 97%), m.p. 105–106 °C,  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 2.30 (2 H, m, H-2e and H-2a), 2.98 (3 H, s, MeSO<sub>2</sub>), 3.47 (3 H, s, 1-OMe), 3.60 (2 H, d, *J* 4 Hz, 6-CH<sub>2</sub>), 4.50 (1 H, m, H-5a), 4.91 (1 H, dd, *J*<sub>1e,2e</sub> 1, *J*<sub>1e,2a</sub> 3 Hz, H-1e), 5.16 (1 H, dd, *J*<sub>3e,4a</sub> 3, *J*<sub>4a,5a</sub> 10 Hz, H-4a), 5.34 (1 H ddd, *J*<sub>4e,4a</sub> = *J*<sub>2e,3e</sub> = 3, *J*<sub>2a,3e</sub> 6 Hz, H-3e), 7.60 (3 H, m, Ar), and 8.10 (2 H, m, Ar).

*Methyl 4-O-Benzoyl-2,6-dideoxy-3-O-methanesulphonyl- $\alpha$ -D-ribo-hexopyranoside* (16).—A mixture of methyl 4-*O*-



benzoyl-6-bromo-2,6-dideoxy-3-*O*-methanesulphonyl- $\alpha$ -*D*-ribo-hexopyranoside (15) (7.1 g), barium carbonate (7.1 g), and 10% palladium-charcoal (6 g) in methanol (600 ml) was hydrogenated for 60 h, and the solution then filtered and evaporated. The resulting syrup was dissolved in dichloromethane and the solution was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. Crystallization from ether-hexane gave methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-methanesulphonyl- $\alpha$ -*D*-ribo-hexopyranoside (16) 5.7 g, 98%, m.p. 93–94 °C;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.27 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 2.30 (2 H, m, H-2a and H-2e), 3.00 (3 H, s,  $\text{MeSO}_2$ ), 3.45 (3 H, s, 1-OMe), 4.25 (1 H, m, H-5a), 4.76 (1 H, dd,  $J_{1e,2e} = J_{1e,2a} = 2$  Hz, H-1e), 4.92 (1 H, dd,  $J_{3e,4a} = 3$ ,  $J_{4a,5a} = 10$  Hz, H-4a), 5.23 (1 H, ddd,  $J_{2e,3e} = J_{3e,4a} = 3$ ,  $J_{2a,3e} = 6$  Hz, H-3e), 7.60 (3 H, m, Ar), and 8.10 (2 H, m, Ar).

*Methyl 3-Azido-4-O-benzoyl-2,3,6-trideoxy- $\alpha$ -D-arabino-hexopyranoside* (17).—A mixture of methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-methanesulphonyl- $\alpha$ -*D*-ribo-hexopyranoside (16) (5.5 g) and sodium azide (2.4 g) was heated in anhydrous dimethylformamide (dmf) (150 ml) at 100–110 °C for 48 h. The solution was filtered, diluted with water, extracted with benzene, and the organic layer dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness. The residue, in benzene, was filtered through a silica gel column to give methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy- $\alpha$ -*D*-arabino-hexopyranoside (17) (3.7 g, 80%) as a colourless oil;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.27 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.80–2.40 (2 H, m, H-2a and H-2e), 3.55 (3 H, s, 1-OMe), 3.70–4.20 (2 H, m, H-3a and H-5a), 4.85 (1 H, m, H-1e), 4.98 (1 H, dd,  $J_{3a,4a} = J_{4a,5a} = 10$  Hz, H-4a), 7.60 (3 H, m, Ar), and 8.10 (2 H, m, Ar).

*Methyl 3-Azido-2,3,6-trideoxy-4-O-methanesulphonyl- $\alpha$ -D-arabino-hexopyranoside* (19).—A solution of methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy- $\alpha$ -*D*-arabino-hexopyranoside (17) (3.7 g) in anhydrous methanol (250 ml) containing sodium methoxide (0.3 g) was stirred at 25 °C for 60 h. After neutralization with Amberlite MB-3 resin and concentration, the residue was dissolved in dichloromethane, dried ( $\text{Na}_2\text{SO}_4$ ), and filtered through a silica gel column to give methyl 3-azido-2,3,6-trideoxy- $\alpha$ -*D*-arabino-hexopyranoside (18) (1.45 g, 61%) as an oil. Some (17) (0.4 g) was also recovered. The alcohol (18) (1.4 g) and methanesulphonyl chloride (5 ml) were dissolved in pyridine (15 ml) at 0 °C and the mixture was set aside at 25 °C for 16 h. The mixture was worked-up in the usual way and filtered through a silica gel column to give methyl 3-azido-2,3,6-trideoxy-4-*O*-methanesulphonyl- $\alpha$ -*D*-arabino-hexopyranoside (19) (1.5 g, 76%), m.p. 60–62 °C;  $[\alpha]_{\text{D}}^{27} + 127.0^\circ$  ( $\text{CH}_3\text{OH}$ ,  $c$  0.8);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.38 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.70–2.50 (2 H, m, H-2a and H-2e), 3.20 (3 H, s,  $\text{MeSO}_2$ ), 3.38 (3 H, s, 1-OMe), 3.50–4.10 (2 H, m, H-3a and H-5a), 4.23 (1 H, dd,  $J_{3a,4a} = J_{4a,5a} = 9$  Hz, H-4a), and 4.82 (1 H, m, H-1e).

*Methyl 3-Azido-2,3,6-trideoxy- $\alpha$ -D-lyxo-hexopyranoside* (21).—Methyl 3-azido-2,3,6-trideoxy-4-*O*-methanesulphonyl- $\alpha$ -*D*-arabino-hexopyranoside (19) (1.25 g) and sodium benzoate (2.9 g) were dissolved in anhydrous DMF (100 ml) and the mixture was stirred at 130–140 °C for 6 d. The mixture was filtered, the solid residue was washed with dichloromethane, and the combined filtrates were evaporated to dryness. The residue was dissolved in dichloromethane, washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and filtered through a silica gel column to give methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy- $\alpha$ -*D*-lyxo-hexopyranoside (20) (1.1 g, 80%) as an oil. A solution of the benzoate (20) (0.38 g) in anhydrous methanol (75 ml) containing sodium meth-

oxide (150 mg) was stirred at 25 °C for 7 d. After neutralization with Amberlite MB-3 resin and concentration, dichloromethane was added to the residue, the solution was dried ( $\text{Na}_2\text{SO}_4$ ), and filtered through a silica gel column to give methyl 3-azido-2,3,6-trideoxy- $\alpha$ -*D*-lyxo-hexopyranoside (21) (0.22 g, 92%) as an oil;  $[\alpha]_{\text{D}}^{22} + 150.0^\circ$  ( $\text{CH}_3\text{OH}$ ,  $c$  0.8);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.28 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.80–2.10 (2 H, m, H-2a and H-2e), 3.35 (3 H, s, 1-OMe), 3.60–4.10 (3 H, m, H-3a, H-4e, and H-5a), and 4.73 (1 H, m, H-1e).

*Methyl 2,3,6-Trideoxy-3-dimethylamino- $\alpha$ -D-lyxo-hexopyranoside (Methyl  $\alpha$ -D-Rhodaminide)* (7).—A mixture of methyl 3-azido-2,3,6-trideoxy- $\alpha$ -*D*-lyxo-hexopyranoside (21) (110 mg) and 10% palladium-charcoal (100 mg) in methanol (25 ml) containing 40% formaldehyde (1 ml) was hydrogenated for 17 h. The solution was filtered and evaporated, and the resulting syrup dissolved in dichloromethane, washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. Preparative t.l.c. on silica gel using 15% methanol in dichloromethane as the eluant gave methyl  $\alpha$ -*D*-rhodaminide (7) (70 mg, 63%) as an oil;  $[\alpha]_{\text{D}}^{22} + 114.0^\circ$  ( $\text{CH}_3\text{OH}$ ,  $c$  1.6);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.32 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.50–1.90 (2 H, m, H-2a and H-2e), 2.30 (6 H, s, 3-NMe<sub>2</sub>), 3.05 (1 H, m, H-4e), 3.36 (3 H, s, 1-OMe), 3.60–4.10 (2 H, m, H-3a and H-5a), and 4.86 (1 H, dd,  $J_{1e,2e} = J_{1e,2a} = 5$  Hz, H-1e).

*Methyl 3-Azido-4-O-benzoyl-2,3,6-trideoxy- $\beta$ -D-arabino-hexopyranoside* (23).—To a solution of methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-methanesulphonyl- $\alpha$ -*D*-ribo-hexopyranoside (16) (1.5 g) in methanol (50 ml), was added 2% hydrogen chloride in methanol (55 ml) and the mixture was refluxed for 2 h. The solution was neutralized with Amberlite IRA-45 resin and evaporated to dryness. The residue was dissolved in dichloromethane, washed with water, and the organic layer was evaporated yielding an oil (1.45 g), chromatography of which on a silica gel column, using dichloromethane as eluant, afforded methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-methanesulphonyl- $\beta$ -*D*-ribo-hexopyranoside (22) (0.75 g), a mixture of (16) and (22) (0.4 g), and (16) (0.27 g). A mixture of (22) (0.75 g) and sodium azide (0.37 g) in anhydrous DMF (25 ml) was heated at 110 °C for 24 h. The mixture was filtered, diluted with water, and extracted with benzene, the organic layer dried ( $\text{Na}_2\text{SO}_4$ ), and then evaporated to dryness. Chromatography on a silica gel column using ethyl acetate-dichloromethane (1 : 10) as the eluant gave methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy- $\beta$ -*D*-arabino-hexopyranoside (23) (0.55 g, 33%), which crystallized from ether-hexane, m.p. 88–90 °C;  $[\alpha]_{\text{D}}^{22} - 80.0^\circ$  ( $\text{CH}_3\text{OH}$ ,  $c$  1.1);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.25 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me) 1.70–2.60 (2 H, m, H-2a and H-2e), 3.45 (3 H, s, 1-OMe), 3.40–4.00 (2 H, m, H-3a and H-5a), 4.43 (1 H, dd,  $J_{1a,2e} = 2$ ,  $J_{1a,2a} = 9$  Hz, H-1a), 4.83 (1 H, dd,  $J_{3a,4a} = J_{4a,5a} = 9$  Hz, H-4a), 7.40 (3 H, m, Ar), and 8.00 (2 H, m, Ar).

*Methyl 3-Azido-2,3,6-trideoxy- $\beta$ -D-arabino-hexopyranoside* (24).—A solution of methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy- $\beta$ -*D*-arabino-hexopyranoside (23) (1.2 g) in anhydrous methanol (100 ml) containing sodium methoxide (0.5 g) was stirred at 25 °C for 16 h. After neutralization with Amberlite MB-3 resin and concentration, the residue was dissolved in dichloromethane, dried ( $\text{Na}_2\text{SO}_4$ ), and filtered through a silica gel column to give crystalline methyl 3-azido-2,3,6-trideoxy- $\beta$ -*D*-arabino-hexopyranoside (24) (0.71 g, 92%), m.p. 73–74 °C;  $[\alpha]_{\text{D}}^{22} - 24.0^\circ$  ( $\text{CH}_3\text{OH}$ ,  $c$  0.5);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.35 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.60–2.40 (2 H, m, H-2a and H-2e), 3.45 (3 H, s, 1-OMe), 3.10–3.60 (3 H, m, H-3a, H-4a, and H-5a), and 4.40 (1 H, dd,  $J_{1a,2e} = 2$ ,  $J_{1a,2a} = 9$  Hz, H-1a).

*Methyl 3-Azido-2,3,6-trideoxy-4-O-methanesulphonyl-β-D-arabino-hexopyranoside* (25).—Methyl 3-azido-2,3,6-trideoxy-β-D-arabino-hexopyranoside (24) (0.45 g) was treated in pyridine (10 ml) at 0 °C with methanesulphonyl chloride (2 ml) and the reaction mixture was set aside at 25 °C for 16 h. Work-up in the usual way and chromatography on a silica gel column (dichloromethane as eluant) gave crystalline methyl 3-azido-2,3,6-trideoxy-4-O-methanesulphonyl-β-D-arabino-hexopyranoside (25) (0.5 g, 78%), m.p. 94–95 °C;  $[\alpha]_D^{22} -38.0^\circ$  (CH<sub>3</sub>OH, *c* 1.00);  $\delta_H$  (CDCl<sub>3</sub>) 1.38 (3 H, d, *J*<sub>5a,6</sub> 6 Hz, 6-Me), 1.60–2.50 (2 H, m, H-2a and H-2e), 3.10 (3 H, s, MeSO<sub>2</sub>), 3.42 (3 H, s, 1-OMe), 3.20–3.80 (2 H, m, H-3a and H-5a), 4.10 (1 H, dd, *J*<sub>3a,4a</sub> = *J*<sub>4a,5a</sub> = 8 Hz, H-4a), and 4.37 (1 H, dd, *J*<sub>1a,2e</sub> 2.5, *J*<sub>1a,2a</sub> 9 Hz, H-1a).

*Methyl 3-Azido-4-O-benzoyl-2,3,6-trideoxy-β-D-lyxo-hexopyranoside* (26).—Methyl 3-azido-2,3,6-trideoxy-4-O-methanesulphonyl-β-D-arabino-hexopyranoside (25) (0.52 g) and sodium benzoate (1.2 g) were dissolved in anhydrous dmf (40 ml) and the mixture was stirred at 140 °C for 5 d. The solution was filtered, the solid residue washed with dichloromethane, the combined filtrates evaporated to dryness, and the residue dissolved in dichloromethane, washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and filtered through a silica gel column to give methyl 3-azido-4-O-benzoyl-2,3,6-trideoxy-β-D-lyxo-hexopyranoside (26) (0.31 g, 54%) as an oil;  $\delta_H$  (CDCl<sub>3</sub>) 1.26 (3 H, d, *J*<sub>5a,6</sub> 6 Hz, 6-Me), 1.40–2.00 (2 H, m, H-2a and H-2e), 3.53 (3 H, s, 1-OMe), 3.20–4.20 (2 H, m, H-3a and H-5a), 4.47 (1 H, dd, *J*<sub>1a,2e</sub> 3, *J*<sub>1a,2a</sub> 9 Hz, H-1a), 5.30 (1 H, dd, *J*<sub>3a,4e</sub> = *J*<sub>4e,5a</sub> = 3 Hz, H-4e), 7.50 (3 H, m, Ar), and 8.10 (2 H, s, Ar).

*Methyl 2,3,6-Trideoxy-3-dimethylamino-β-D-lyxo-hexopyranoside* (*Methyl β-D-Rhodaminide*) (8).—A solution of methyl 3-azido-4-O-benzoyl-2,3,6-trideoxy-β-D-lyxo-hexopyranoside (26) (0.28 g) in anhydrous methanol (20 ml) containing sodium methoxide (100 mg) was stirred at 25 °C for 16 h. After neutralization with Amberlite MB-3 resin and concentration, dichloromethane was added to the residue. The solution was dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered through a silica gel column to give methyl 3-azido-2,3,6-trideoxy-β-D-lyxo-hexopyranoside (27) contaminated with the corresponding furanoside (0.16 g). Without purification the mixture and 10% palladium-charcoal (120 mg) in methanol containing 40% formaldehyde (1 ml) was hydrogenated for 17 h. The solution was filtered and evaporated, the residue dissolved in dichloromethane, washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. Preparative t.l.c. of the residue on silica gel (15% methanol in dichloromethane as eluant) gave methyl β-D-rhodaminide (8) (110 mg, 61%) as an oil;  $[\alpha]_D^{22} -38.0^\circ$  (CH<sub>3</sub>OH, *c* 1.0);  $\delta_H$  (CDCl<sub>3</sub>) 1.38 (3 H, d, *J*<sub>5a,6</sub> 6 Hz, 6-Me), 1.50–2.10 (2 H, m, H-2a and H-2e), 2.3 (6 H, s, 3-NMe<sub>2</sub>), 2.93 (1 H, m, H-4e), 3.47 (3 H, s, 1-OMe), 3.20–3.60 (2 H, m, H-3a and H-5a), and 4.30 (1 H, dd, *J*<sub>1a,2e</sub> 3, *J*<sub>1a,2a</sub> 9 Hz, H-1a).

*4''-O-(4-Iodobenzoyl)-megalomicin A* (6).—Megalomicin A (1) (3 g) was dissolved in acetone (100 ml) and sodium bicarbonate (0.86 g) and 4-iodobenzoyl chloride (2.01 g) were added. The mixture was stirred at 25 °C in the dark for 5 h. The mixture was evaporated to dryness, taken up in chloroform, washed with water, and the chloroform solution evaporated to dryness. Chromatography of the residue on a silica gel column (110 × 2.5 cm) (15% methanol in chloroform as eluant) gave 4''-O-(4-iodobenzoyl)megalomicin A (6) (1.56 g, 41%) which was crystallized several times from aqueous acetone, m.p. 150–155 °C (Found: C, 53.6; H, 7.6; N, 2.4; I, 11.20. C<sub>51</sub>H<sub>83</sub>I<sub>N</sub><sub>2</sub>O<sub>16</sub>·2H<sub>2</sub>O

requires C, 53.60; H, 7.7; N, 2.45; I, 11.10%);  $[\alpha]_D -84.1^\circ$  (CHCl<sub>3</sub>); p*K*<sub>a</sub> 8.3;  $\nu_{\max}$  (CCl<sub>4</sub>) 3 500, 2 760, 1 730, 1 710, 1 685, and 1 260 cm<sup>-1</sup>; *m/e* 1 106 (*M*<sup>+</sup>);  $\delta_H$  (CDCl<sub>3</sub>) 0.88 (3 H, d, *J* 7 Hz, 2-Me), 0.92 (3 H, t, *J* 7 Hz, 14-Me), 1.62 (3 H, s, 6-Me), 2.26 (6 H, s, 3''-NMe<sub>2</sub>), 2.34 (6 H, s, 3'''-NMe<sub>2</sub>), 7.71 (2 H, d, *J* 8 Hz, Ar), and 8.09 (2 H, d, *J* 8 Hz, Ar).

*Methyl 4,6-O-Benzylidene-2-deoxy-3-O-methanesulphonyl-α-D-lyxo-hexopyranoside* (48).—Methyl 4,6-O-benzylidene-2-deoxy-α-D-lyxo-hexopyranoside (47) (9.8 g)<sup>25,26</sup> was dissolved in pyridine (100 ml) and methanesulphonyl chloride (20.9 g) was added dropwise during 0.5 h. The mixture was stirred at 25 °C for 18 h and then concentrated to afford methyl 4,6-O-benzylidene-2-deoxy-3-O-methanesulphonyl-α-D-lyxo-hexopyranoside (48) (8.8 g, 69%) as colourless crystals (from ethanol), m.p. 114–115 °C (decomp.) (Found: C, 52.6; H, 6.0; N, 9.2. C<sub>15</sub>H<sub>20</sub>O<sub>7</sub>S requires C, 52.3; H, 5.85; N, 9.3%); *m/e* 344 (*M*<sup>+</sup>);  $[\alpha]_D +176.3^\circ$  (CHCl<sub>3</sub>);  $\nu_{\max}$  (KBr) 1 345 and 1 190 cm<sup>-1</sup>;  $\delta_H$  (CDCl<sub>3</sub>) 1.98 (1 H, ddd, *J*<sub>1e,2e</sub> 2, *J*<sub>2e,2a</sub> 15, and *J*<sub>2e,3a</sub> 5 Hz, H-2e), 2.40 (1 H, ddd, *J*<sub>1e,2a</sub> 3.5, *J*<sub>2e,2a</sub> = *J*<sub>2a,3a</sub> = 15 Hz, H-2a), 3.03 (3 H, s, OSO<sub>2</sub>Me), 3.37 (3 H, s, OMe), 3.65 (1 H, dd, *J*<sub>4e,5a</sub> = *J*<sub>5a,6</sub> 2 Hz, H-5a), 4.03 (1 H, dd, *J*<sub>5a,6</sub> 2, *J*<sub>6,6'</sub> 16 Hz, H-6), 4.31 (1 H, dd, *J*<sub>5a,6</sub> 2, *J*<sub>6,6'</sub> 16 Hz, H-6'), 4.40 (1 H, dd, *J*<sub>2e,3a</sub> 5, *J*<sub>3a,4e</sub> 3.5 Hz, H-4e), 5.00 (1 H, dd, *J*<sub>1e,2e</sub> 2, *J*<sub>1e,2a</sub> 3.5 Hz, H-1e), 5.18 (1 H, ddd, *J*<sub>2e,3a</sub> 5, *J*<sub>2a,3a</sub> 15, and *J*<sub>3a,4e</sub> 3.5 Hz, H-3a), 5.62 (1 H, s, PhCH), and 7.40 (5 H, m, PhCH).

*Methyl 4-O-Benzoyl-6-bromo-2,6-dideoxy-3-O-methanesulphonyl-α-D-lyxo-hexopyranoside* (49).—Methyl 4,6-O-benzylidene-2-deoxy-3-O-methanesulphonyl-α-D-lyxo-hexopyranoside (48) (1 g) was dissolved in dry carbon tetrachloride (50 ml) and dry 1,1,2,2-tetrachloroethane (3 ml). *N*-Bromosuccinimide (738 mg) and barium carbonate (0.4 g) were added and the mixture was refluxed in an argon atmosphere for 2.5 h. The hot solution was filtered and the solid was washed with hot carbon tetrachloride (120 ml). The combined filtrates were evaporated to dryness and the resulting syrup was dissolved in ether, washed with water, dried (MgSO<sub>4</sub>), evaporated to dryness, and the resulting syrup was chromatographed on a silica gel column (20 × 2 cm) (chloroform as eluant) to give methyl 4-O-benzoyl-6-bromo-2,6-dideoxy-3-O-methanesulphonyl-α-D-lyxo-hexopyranoside (49) (0.92 g, 75%) as a colourless oil (Found: C, 41.9; H, 4.70, S, 6.0. C<sub>15</sub>H<sub>19</sub>BrO<sub>5</sub>S requires C, 42.55; H, 4.5, S, 7.6, *m/e* 422 (*M*<sup>+</sup>);  $[\alpha]_D +100.7^\circ$  (CHCl<sub>3</sub>);  $\nu_{\max}$  (liquid film) 2 940, 1 730, 1 250, 1 350, and 1 175 cm<sup>-1</sup>;  $\delta_H$  (CDCl<sub>3</sub>) 2.15–2.45 (2 H, m, 2-CH<sub>2</sub>), 3.02 (3 H, s, OSO<sub>2</sub>Me), 3.32 (1 H, m, 6-CH<sub>2</sub>), 3.47 (3 H, s, OMe), 4.20 (1 H, m, *J*<sub>5a,6</sub> 7 Hz, H-5a), 5.02 (1 H, dd, *J*<sub>1e,2e</sub> 2, *J*<sub>1e,2a</sub> 3.5 Hz, H-1e), 5.28 (1 H, ddd, *J*<sub>2e,3a</sub> 5, *J*<sub>2a,3a</sub> 15, and *J*<sub>3a,4e</sub> 3.5 Hz, H-3a), 5.75 (1 H, m, H-4e), and 7.52 and 8.10 (5 H, m, OCOPh).

*Methyl 4-O-Benzoyl-2,6-dideoxy-3-O-methanesulphonyl-α-D-lyxo-hexopyranoside* (50).—Methyl 4-O-benzoyl-6-bromo-2,6-dideoxy-3-O-methanesulphonyl-α-D-lyxo-hexopyranoside (49) (820 mg) and tributylstannane (11 g) were dissolved in dry benzene (100 ml) and the mixture was refluxed for 24 h. The solution was concentrated and the residue was chromatographed on a silica gel column (120 × 2.5 cm.) (chloroform as eluant) to give methyl 4-O-benzoyl-2,6-dideoxy-3-O-methanesulphonyl-α-D-lyxo-hexopyranoside (50) (650 mg, 97%) as a colourless oil (Found: C, 52.5, H, 6.05; N, 9.1. C<sub>16</sub>H<sub>20</sub>O<sub>5</sub>S requires C, 52.3; H, 5.85; N, 9.3%); *m/e* 313 (*[M - OMe]*<sup>+</sup>),  $[\alpha]_D +173.3^\circ$  (CHCl<sub>3</sub>);

$\nu_{\max}$  (CHCl<sub>3</sub>) 2 900, 1 725, 1 340, 1 260, 1 175, and 1 045 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.22 (3 H, d,  $J_{5a,6}$  7 Hz, 6-Me), 2.13—2.50 (2 H, m, 2-CH<sub>2</sub>), 3.00 (3 H, s, OSO<sub>2</sub>Me), 3.39 (3 H, s, OMe), 4.15 (1 H, m,  $J_{5a,6}$  7 Hz, H-5a), 4.97 (1 H, dd,  $J_{1e,2e}$  2,  $J_{1e,2a}$  3.5 Hz, H-1e), 5.30 (1 H, ddd,  $J_{2e,3a}$  5,  $J_{2a,3a}$  15, and  $J_{3a,4e}$  3.5 Hz, H-3a), 5.52 (1 H, m, H-4e), and 7.55 and 8.15 (5 H, m, OCOPh).

*Methyl 3-Azido-4-O-benzoyl-2,3,6-trideoxy- $\alpha$ -D-xylo-hexopyranoside (51)*.—Methyl 4-O-benzoyl-2,6-dideoxy-3-O-methanesulphonyl- $\alpha$ -D-lyxo-hexopyranoside (50) (412 mg) and sodium azide (400 mg) were dissolved in wet DMF (3 ml) and the mixture refluxed at 100 °C for 49 h. Additional sodium azide (400 mg) was added and the reaction was continued for a further 40 h. The mixture was poured into water (25 ml) and extracted with chloroform, and the chloroform extracts washed with water and then evaporated to dryness. Chromatography of the residue on a silica gel column (120  $\times$  2 cm) (chloroform as eluant) gave methyl 3-azido-4-O-benzoyl-2,3,6-trideoxy- $\alpha$ -D-xylo-hexopyranoside (51) (54 mg, 15%) as a colourless oil;  $m/e$  290.113 9 ( $M^{+} - 1$ ) (C<sub>14</sub>H<sub>16</sub>N<sub>3</sub>O<sub>4</sub> requires  $M - 1$  290.114 1);  $[\alpha]_{\text{D}} + 135.3^{\circ}$  (CHCl<sub>3</sub>);  $\nu_{\max}$  (CCl<sub>4</sub>) 2 900, 2 110, 1 725, 1 260, and 1 040 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.21 (3 H, d,  $J_{5a,6}$  7 Hz, 6-Me), 1.98—2.25 (2 H, m, 2-CH<sub>2</sub>), 3.43 (3 H, s, OMe), 3.99 (1 H, ddd,  $J_{2a,3e} = J_{3e,4e} = 3$ ,  $J_{2a,3e}$  4 Hz, H-3e), 4.38 (1 H, dq,  $J_{4e,5a}$  2,  $J_{5a,6}$  7 Hz, H-5a), 4.84 (2 H, m, H-1 and H-4), and 7.53 and 8.09 (5 H, m, OCOPh).

*Methyl 2,3,6-Trideoxy-3-dimethylamino- $\alpha$ -D-xylo-hexopyranoside (40)*.—Methyl 3-azido-4-O-benzoyl-2,3,6-trideoxy- $\alpha$ -D-xylo-hexopyranoside (51) (158 mg) was dissolved in methanol (20 ml) and sodium methoxide (0.1N, 1.1 equiv.) (6 ml) was added. The mixture was stirred at 25 °C for 20 h and then concentrated to 10 ml. A solution of formaldehyde (37%, 0.44 ml) and 10% palladium-charcoal (95 mg) were added and the mixture was hydrogenated at 55 lb in<sup>-2</sup> at 25 °C for 18 h. The catalyst was filtered off and the filtrate and washings were combined and evaporated to dryness. Chromatography of the residue on a silica gel column (110  $\times$  2.5 cm) (methanol-chloroform (1:9) as eluant) gave methyl 2,3,6-trideoxy-3-dimethylamino- $\alpha$ -D-xylo-hexopyranoside (40) (44 mg, 43%) as an oil (Found:  $m/e$  189.136 1 ( $M^{+}$ ); C<sub>9</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub> requires  $M$  189.136 4);  $[\alpha]_{\text{D}} + 99.0^{\circ}$  (CHCl<sub>3</sub>);  $[\theta]_{295} - 1 726$  (TA-Cu);  $\nu_{\max}$  (liquid film) 3 375, 2 925, 2 775, and 1 045 cm<sup>-1</sup>.

(9S)-2',4'',9,11-Tetra-O-benzoyl-9-dihydromegalalosamine (63).—(9S)-9-Dihydromegalalosamine (62) and benzoic anhydride (5 g) were dissolved in dry pyridine (50 ml) and the mixture was refluxed for 16 h. The excess of anhydride was destroyed by addition of methanol and the mixture was evaporated to dryness and azeotroped with toluene. Preparative t.l.c. on silica gel plates [methanol-chloroform (1:9) as eluant] gave (9S)-2',4'',9,11-tetra-O-benzoyl-9-dihydromegalalosamine (63) (1.71 g, 55%) as a colourless amorphous solid (Found: C, 65.4; H, 7.85; N, 2.10. C<sub>65</sub>H<sub>86</sub>N<sub>2</sub>O<sub>16</sub>·2H<sub>2</sub>O requires C, 65.8; H, 7.6; N, 2.4%);  $[\alpha]_{\text{D}} - 10.5^{\circ}$  (CH<sub>3</sub>OH);  $\nu_{\max}$  (CHCl<sub>3</sub>) 3 470, 2 780, 1 750, 1 270, and 707 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 0.53 (3 H, s, 12-Me), 0.74 (3 H, t,  $J$  7.5 Hz, 14-Me), 0.80 (3 H, d,  $J$  7.5 Hz, Me), 1.00 (3 H, d,  $J$  7.5 Hz, Me), 1.03 (3 H, d,  $J$  7.5 Hz, Me), 1.09 (3 H, d,  $J$  7.5 Hz, Me), 1.25 (3 H, d,  $J$  6 Hz, Me), 1.42 (3 H, d,  $J$  7.5 Hz, Me), 1.48 (3 H, s, 6-Me), 2.39 (6 H, s, 3'-NMe<sub>2</sub>), 2.43 (6 H, s, 3''-NMe<sub>2</sub>), 7.25—7.52 (12 H, m, OCOPh), 7.80 (4 H, d,  $J$  9 Hz, OCOPh), 8.00 (2 H, d,  $J$  9 Hz, OCOPh), and 8.20 (2 H, d,  $J$  9 Hz, OCOPh).

2',4''-Di-O-benzoylmegalalosamine (64).—Megalalosamine

(59) (2.5 g) was dissolved in acetone (50 ml). Sodium bicarbonate (1.5 g) and benzoyl chloride (0.75 ml) were added and the mixture was stirred at 25 °C for 16 h. The mixture was filtered and the residue was washed with acetone. The acetone filtrate was slowly added to a solution of aqueous ammonium hydroxide (5%), and the precipitate was filtered off and chromatographed on a silica gel column (160  $\times$  2.5 cm) [methanol-chloroform (3:97) as eluant] to give 2',4''-di-O-benzoylmegalalosamine (64) (1.82 g, 57%) which crystallized from hexane, m.p. 221—224 °C (Found: C, 62.9; H, 8.00; N, 2.9. C<sub>51</sub>H<sub>76</sub>N<sub>2</sub>O<sub>14</sub>·2H<sub>2</sub>O requires C, 62.7; H, 8.25; N, 2.9%);  $m/e$  940 ( $M^{+}$ ),<sup>6</sup>  $[\alpha]_{\text{D}} - 32.1^{\circ}$  (C<sub>2</sub>H<sub>5</sub>OH);  $pK_{\text{a}}$  7.3;  $\nu_{\max}$  (CCl<sub>4</sub>) 3 470, 2 770, 1 730, 1 720, 1 690, 1 270, 1 170, and 712 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 0.66 (3 H, d,  $J$  7.5 Hz, Me), 0.81 (3 H, d,  $J$  7.5 Hz, Me), 0.83 (3 H, t,  $J$  7.5 Hz, 14-Me), 1.03 (3 H, s, 12-Me), 1.10 (3 H, d,  $J$  7.5 Hz, Me), 1.12 (3 H, d,  $J$  7.5 Hz, Me), 1.21 (3 H, s, 6-Me), 1.32 (3 H, d,  $J$  7.5 Hz, Me), 1.44 (3 H, s, 6-Me), 2.16 (6 H, s, 3'-NMe<sub>2</sub>), 2.31 (6 H, s, 3''-NMe<sub>2</sub>), 5.23 (1 H, dd,  $J_{13,14}$  10,  $J_{13,14'}$  2.5 Hz, H-13), 7.27—7.58 (6 H, m, OCOPh), 8.09 (2 H, d,  $J$  9 Hz, OCOPh), and 8.35 (2 H, d,  $J$  9 Hz, OCOPh).

3-O-Acetyl-2',4''-di-O-benzoylmegalalosamine (65).—2',4''-Di-O-benzoylmegalalosamine (64) (2 g) was dissolved in dry pyridine (20 ml) and acetic anhydride (7 ml) was added. The mixture was refluxed for 16 h, and then poured into ice-water and extracted with chloroform. The chloroform extract was washed with water, dried (MgSO<sub>4</sub>), evaporated to dryness, and chromatography of the residue on a silica gel column (160  $\times$  2.5 cm) [methanol-chloroform (3:97) as eluant] gave 3-O-acetyl-2',4''-di-O-benzoylmegalalosamine (65) (800 mg, 38%) as an amorphous solid (Found: C, 64.6; H, 7.9, N, 2.6. C<sub>53</sub>H<sub>78</sub>N<sub>2</sub>O<sub>15</sub> requires C, 64.75; H, 7.9; N, 2.85%);  $m/e$  982 ( $M^{+}$ ), 860 ( $[M - 122]^{+}$ ), 818 ( $[M - 122 - 42]^{+}$ ), 803 (o'),<sup>6</sup> 721 (f', j'), 720 (e', i'), 705 (h', l'), 704 (g', k'), 278 (q, r), and 262 (m, n);  $[\alpha]_{\text{D}} - 15.6^{\circ}$  (C<sub>2</sub>H<sub>5</sub>OH);  $\nu_{\max}$  (CCl<sub>4</sub>) 3 470, 2 770, 1 750, 1 730, 1 720, 1 650, 1 270, 1 170, and 709 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 0.65 (3 H, d,  $J$  7 Hz, Me), 0.73 (3 H, d,  $J$  7.5 Hz, Me), 0.80 (3 H, t,  $J$  7.5 Hz, 14-Me), 1.05 (3 H, s, 12-Me), 1.10 (3 H, d,  $J$  6.5 Hz, Me), 1.11 (3 H, d,  $J$  7 Hz, Me), 1.22 (3 H, d,  $J$  6 Hz, Me), 1.33 (3 H, d,  $J$  7 Hz, Me), 1.42 (3 H, s, 6-Me), 2.08 (3 H, s, 3-OAc), 2.27 (6 H, s, 3'-NMe<sub>2</sub>), 2.43 (6 H, s, 3''-NMe<sub>2</sub>), 5.24 (1 H, dd,  $J_{13,14}$  11,  $J_{13,14'}$  2 Hz, H-13), 5.46 (1 H, dd,  $J_{2,3}$  11.5,  $J_{3,4}$  1 Hz, H-3), 7.24—7.59 (6 H, m, OCOPh), 8.03 (2 H, d,  $J$  9 Hz, OCOPh), and 8.35 (2 H, d,  $J$  9 Hz, OCOPh).

*Methyl 2,3,6-Trideoxy- $\alpha$ -D-erythro-hexopyranoside (Methyl  $\alpha$ -D-Amicitoside) (73)*.—Methyl 4-O-benzoyl-6-bromo-2,3,6-trideoxy- $\alpha$ -D-erythro-hexopyranoside (72)<sup>36</sup> (6.2 g) dissolved in dry tetrahydrofuran (THF) (30 ml) was added slowly to a suspension of lithium aluminium hydride (2.86 g) in dry THF (70 ml) under N<sub>2</sub> with cooling. The mixture was refluxed for 6 h and then set aside at 25 °C for 16 h. Excess of hydride was quenched with water and ethyl acetate, the reaction mixture was filtered, and the filtrate was concentrated to leave a residue, chromatography of which on a silica gel column (100  $\times$  3 cm) [diethyl ether-dichloromethane (1:9) as eluant] gave methyl 2,3,6-trideoxy- $\alpha$ -D-erythro-hexopyranoside (73) (1.38 g, 50%) as a colourless oil (Found:  $m/e$ , 146.094 6 ( $M^{+}$ ); C<sub>7</sub>H<sub>14</sub>O<sub>3</sub> requires  $M$ , 146.094 2);  $[\alpha]_{\text{D}} + 142.0^{\circ}$  (H<sub>2</sub>O) {lit.,<sup>36</sup>  $[\alpha]_{\text{D}} + 142^{\circ}$  (H<sub>2</sub>O)}; <sup>1</sup>H n.m.r. and i.r. spectra and the b.p. were also identical with those reported.<sup>36</sup>

*Methyl 2,3,6-Trideoxy- $\alpha$ -D-glycero-hexopyran-4-uloside*

(*Methyl  $\alpha$ -D-Cineruloside*) (69).—Ruthenium dioxide dihydrate (700 mg) was added to a solution of sodium metaperiodate (8.7 g) in water (80 ml). After stirring vigorously for 10 min the mixture was extracted with distilled carbon tetrachloride ( $2 \times 25$  ml), and the extract was added slowly to a solution of methyl 2,3,6-trideoxy- $\alpha$ -D-erythro-hexopyranoside (73) (300 mg) in distilled carbon tetrachloride (50 ml) at 0 °C. After 10 min, excess of reagent was quenched with isopropanol and the mixture was filtered. The filtrate was concentrated to a small volume and preparative t.l.c. on silica gel plates [acetone-hexane (1 : 4) as eluant] gave methyl 2,3,6-trideoxy- $\alpha$ -D-glycero-hexopyran-4-uloside (69) (150 mg, 50%) as a colourless oil [Found:  $m/e$ , 144.077 2 ( $M^{+}$ ).  $C_7H_{12}O_3$  requires  $M$ , 144.078 6];  $[\alpha]_D + 306.3^\circ$  ( $CHCl_3$ );  $\nu_{max}$  (film) 1 740  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.30 (3 H, d,  $J_{5a,6}$  6.5 Hz, 6-Me), 1.90–2.60 (4 H, m, H-2a, H-2e, H-3a, and H-3e), 3.43 (3 H, s, OMe), 4.25 (1 H, q,  $J_{5a,6}$  6.5 Hz, H-5a), and 4.85 (1 H, dd,  $J_{1e,2e} = J_{1e,2a} = 4$  Hz, H-1e).

1,5-Anhydro-4,6-O-benzylidene-2,3-dideoxy-D-erythro-hexitol (75).—To a solution of 1,5-anhydro-2,3-dideoxy-D-erythro-hexitol (74) (3.4 g) in dry DMF (30 ml) was added dimethoxytoluene (4.5 g) and *p*-toluenesulphonic acid (16 mg). The mixture was evacuated on the rotary evaporator under reduced pressure for 1 h at 60 °C, then concentrated *in vacuo*, and the residue dissolved in chloroform and washed several times with aqueous sodium bicarbonate solution. The organic fraction was dried, filtered, and concentrated to give 1,5-anhydro-4,6-O-benzylidene-2,3-dideoxy-D-erythro-hexitol (75) (5 g, 89%), m.p. 135 °C (lit.<sup>40</sup> m.p. 135–136 °C) (Found: C, 70.62; H, 7.26.  $C_{13}H_{16}O_3$  requires C, 70.89; H, 7.32%);  $m/e$  220 ( $M^{+}$ );  $[\alpha]_D - 2.8^\circ$  ( $CHCl_3$ ) [lit.<sup>1</sup>  $[\alpha]_D - 3.5^\circ$  ( $CDCl_3$ )];  $\delta_H$  ( $CDCl_3$ ) 1.55–2.20 (4 H, m, H-2a, H-2e, H-3a, and H-3e), 3.15–4.38 (6 H, m, H-1a, H-1e, H-4a, H-5a, H-6a, and H-6e), 5.55 (1 H, s, Ar-CH), and 7.20–7.60 (5 H, m, Ar).

1,5-Anhydro-2,3,6-trideoxy-D-erythro-hexitol (77).—1,5-Anhydro-4,6-O-benzylidene-2,3-dideoxy-D-erythro-hexitol (75) (9.9 g) was dissolved in dry carbon tetrachloride (330 ml), and *N*-bromosuccinimide (9.05 g) and barium carbonate (22 g) were added. The mixture was refluxed for 2 h, then filtered whilst hot, and the filtrate was concentrated, diluted with diethyl ether, and washed with water. The ethereal extract was dried ( $MgSO_4$ ), filtered, and evaporated, and the residual oil was chromatographed on a silica gel column ( $45 \times 3$  cm) (dichloromethane as eluant) to give 1,5-anhydro-4-O-benzoyl-6-bromo-2,3,6-trideoxy-D-erythro-hexitol (76) (9.6 g, 73%);  $m/e$  205 [ $M - 94$ ]<sup>+</sup>;  $\nu_{max}$  (film) 1 715  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.40–2.50 (4 H, m, H-2a, H-2e, H-3a, and H-3e), 3.30–4.45 (5 H, m, H-1a, H-1e, H-5a, H-6a, and H-6e), 4.75–5.05 (1 H, m, H-4a), 7.30–7.60 (3 H, m, Ar), and 7.95–8.20 (2 H, m, Ar). The hexitol (76) (9.6 g) was dissolved in dry THF (100 ml) and the solution was added slowly to a stirred suspension of lithium aluminium hydride (4.9 g) in dry THF (150 ml) at 0 °C. The mixture was refluxed for 16 h, cooled, and the excess of hydride was quenched with ethyl acetate and water. After filtration the filtrate was evaporated, and chromatography of the resulting oil on a silica gel column ( $110 \times 3$  cm) [diethyl ether-dichloromethane (5 : 95) as eluant] gave 1,5-anhydro-2,3,6-trideoxy-D-erythro-hexitol (77) (1.1 g, 30%) as a colourless oil, b.p. 100 °C at 15 mmHg (bath) (Found: C, 62.53; H, 10.73.  $C_6H_{12}O_2$  requires C, 62.04; H, 10.42%);  $m/e$  116 ( $M^{+}$ );  $[\alpha]_D + 22.1^\circ$  ( $CHCl_3$ );  $\nu_{max}$  (film) 3 400  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.28 (3 H, d,  $J_{5a,6}$  6 Hz,

6-Me), 1.50–2.20 (4 H, m, H-2a, H-2e, H-3a, and H-3e), 2.52 (1 H, br, s, OH), 2.98–3.50 (3 H, m, H-1a, H-1e, and H-5a), and 3.75–4.02 (1 H, m, H-4a).

1,5-Anhydro-2,3,6-trideoxy-D-glycero-hexitol-4-ulose (78).—Ruthenium dioxide dihydrate (1.5 g) was added to a solution of sodium meta-periodate (16 g) in water (160 ml). After stirring vigorously for 10 min, the mixture was extracted with distilled carbon tetrachloride ( $2 \times 25$  ml), and the carbon tetrachloride extract was added slowly to a solution of 1,5-anhydro-2,3,6-trideoxy-D-erythro-hexitol (77) (400 mg) in distilled carbon tetrachloride (100 ml) at 0 °C. After 10 min, excess of reagent was quenched with isopropanol and the mixture was filtered. The filtrate was concentrated to a small volume and preparative t.l.c. on silica gel plates [acetone-hexane (1 : 4) as eluant] gave 1,5-anhydro-2,3,6-trideoxy-D-glycero-hexitol-4-ulose (78) (77 mg, 20%) as a colourless oil [Found:  $m/e$ , 114.067 3 ( $M^{+}$ ).  $C_6H_{10}O_2$  requires  $M$ , 114.068 0];  $[\alpha]_D + 39.2^\circ$  ( $CHCl_3$ );  $\nu_{max}$  1 750  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.32 (3 H, d,  $J_{5a,6}$  6.5 Hz, 6-Me), 1.95–2.25 (2 H, m, H-2a and H-2e), 2.40–2.63 (2 H, m, H-3a and H-3e), 3.60–4.10 (2 H, m, H-1a and H-1e), and 3.95 (1 H, q,  $J_{5a,6}$  6.5 Hz, H-5a).

3,4-Di-O-acetyl-D-xylal (85).—A solution of 1,2,3,4-tetra-O-acetyl- $\beta$ -D-xylopyranose (84)<sup>41</sup> (7.7 g) and titanium tetrabromide (11.0 g) in dry chloroform (200 ml) (passed through alumina) was refluxed for 2 h, cooled, and washed several times with water. The organic layer was then washed with aqueous sodium bicarbonate solution and brine, and then concentrated to leave a brown oil. Sodium acetate (22 g) was dissolved in 50% aqueous acetic acid (60 ml) and the resulting solution was cooled to 0 °C. To this was added zinc powder (17 g) and a solution of copper(II) sulphate pentahydrate (1.7 g) in water (5 ml). This mixture was maintained at 0 °C and upon evolution of hydrogen, the above crude pyranosyl bromide in glacial acetic acid (5 ml) was added dropwise. After 3 h at 0 °C, the mixture was filtered and the filtrate diluted with ice-water, then extracted with three portions of chloroform. The combined chloroform extracts were washed with water, then aqueous sodium bicarbonate solution to remove all acetic acid, water, and brine. The organic fraction was dried ( $MgSO_4$ ), filtered, and concentrated to leave a clear oil, chromatography of which on a silica gel column ( $45 \times 3$  cm) [acetone-hexane (5 : 95) as eluant] gave 3,4-di-O-acetyl-D-xylal (85)<sup>42,43</sup> (1.7 g, 35%) as a colourless oil;  $m/e$  140 [ $M - 60$ ]<sup>+</sup>;  $\nu_{max}$  (film) 1 740 and 1 645  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.87 (3 H, s, OAc), 1.90 (3 H, s, OAc), 3.95 (2 H, m, H-5a and H-5e), 4.84 (3 H, m, H-2, H-3a, and H-4a), and 6.41 (1 H, m, H-1).

*Methyl 2,3-Dideoxy- $\alpha$ -D-glycero-pentopyranoside* (79).—3,4-Di-O-acetyl-D-xylal (85) (1.7 g) was dissolved in dry dichloromethane (40 ml) containing dry methanol (3.8 ml). Boron trifluoride-ether (1/1) (1.05 ml) was added dropwise and the resulting solution was set aside at 25 °C for 1 h. The reaction mixture was washed several times with water, then concentrated to give methyl 4-O-acetyl-2,3-dideoxy- $\alpha$ -D-glycero-pent-2-eno-pyranoside (86) as a colourless oil. This oil was dissolved in methanol (50 ml) and hydrogenated over 10% palladium-charcoal (1 g) at 25 °C for 16 h, filtered, and the filtrate evaporated. The residue was deacetylated with sodium methoxide (1 equiv.) in methanol. After 0.5 h at 25 °C the solution was concentrated and chromatography of the residue on a silica gel column ( $110 \times 2.5$  cm) [methanol-chloroform (2 : 98) as eluant] gave methyl 2,3-dideoxy- $\alpha$ -D-glycero-pentopyranoside (79)

(670 mg, 60%) as a colourless oil [Found:  $m/e$  132.078 4 ( $M^{+}$ ).  $C_6H_{12}O_3$  requires  $M$ , 132.078 5];  $[\alpha]_D^{26} -91.9^\circ$  ( $CHCl_3$ );  $\nu_{max}$  (film) 3 410 and 2 925  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.45–2.18 (4 H, m, H-2a, H-2e, H-3a, and H-3e), 3.38 (3 H, s, 1-OMe), and 4.58 (1 H, m, H-1e).

(2S)-2-Methoxytetrahydropyran-5-ulose (80).—Ruthenium dioxide dihydrate (2.25 g) was added to a solution of sodium metaperiodate (24 g) in water (240 ml). After stirring vigorously for 10 min, the mixture was extracted with distilled carbon tetrachloride ( $2 \times 25$  ml). This extract was added slowly to a solution of methyl 2,3-dideoxy- $\alpha$ -D-glycero-pentopyranoside (79) (500 mg) in distilled carbon tetrachloride (150 ml) at 0 °C. After 10 min, excess of reagent was quenched with isopropanol and the mixture was filtered. The filtrate was concentrated to small volume, and preparative t.l.c. on silica gel plates [acetone–hexane (3 : 7) as eluant] gave (2S)-2-methoxytetrahydropyran-5-ulose (80) (220 mg, 44%) as a colourless oil [Found:  $m/e$  130.062 0 ( $M^{+}$ ).  $C_6H_{10}O_3$  requires  $M$ , 130.062 9];  $[\alpha]_D -140.9^\circ$  ( $CHCl_3$ );  $\nu_{max}$  (film) 1 735  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.80–2.60 (4 H, m, H-2a, H-2e, H-3a, and H-3e), 3.45 (3 H, s, 1-OMe), 4.05 (2 H, AB quartet,  $\Delta\nu$  18 Hz,  $J_{5a,5e}$  16 Hz, H-5a and H-5e), and 4.87 (1 H, dd,  $J_{1e,2a} = J_{1e,2e} = 4$  Hz, H-1e).

3,4-Di-O-acetyl-L-rhamnal (87).—A mixture of 1,2,3,4-tetra-O-acetyl-L-rhamnose<sup>44</sup> (30 g) and titanium tetrabromide (47 g) in chloroform (600 ml) (passed over alumina) was refluxed for 2 h, cooled, and then poured into water. The organic layer was washed several times with water and once with aqueous sodium bicarbonate solution. The solvent was evaporated to leave a yellow gum,  $\delta_H$  ( $CDCl_3$ ) 1.27 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.98 (3 H, s, OAc), 2.07 (3 H, s, OAc), 2.13 (3 H, s, OAc), 4.10 (1 H, dq,  $J_{4a,5a}$  9,  $J_{5a,6}$  6 Hz, H-5a), 5.13 (1 H, dd,  $J_{3a,4a} = J_{4a,5a} = 9$  Hz, H-4a), 5.42 (1 H, dd,  $J_{2,3a}$  3.5,  $J_{1,2}$  1.5 Hz, H-2), 5.65 (1 H, dd,  $J_{3a,4a}$  9,  $J_{2,3a}$  3.5 Hz, H-3a), and 6.23 (1 H, m, H-1). Sodium acetate (92 g) was dissolved in 50% aqueous acetic acid (220 ml) and to the resulting solution, cooled to 0 °C, was added zinc powder (66 g) and a solution of copper(II) sulphate pentahydrate (6.6 g) in water (20 ml). The mixture was maintained at 0 °C and upon evolution of hydrogen, the above crude pyranosyl bromide in glacial acetic acid (10 ml) was added dropwise. After 3 h at 0 °C, the mixture was filtered and the filtrate extracted with three portions of chloroform. The combined chloroform extracts were washed with water, then aqueous sodium bicarbonate solution to remove all acetic acid, water, and saturated sodium chloride solution. The organic fraction was dried ( $MgSO_4$ ), filtered, and concentrated to leave a clear oil, chromatography of which on a silica gel column ( $45 \times 3$  cm) [acetone–hexane (5 : 95) as eluant] gave 3,4-di-O-acetyl-L-rhamnal (87) (18.1 g, 93%) as a colourless oil, b.p. 76 °C at 0.2 mmHg (Found: C, 56.50; H, 6.71.  $C_{10}H_{14}O_5$  requires C, 56.07, H, 6.59%);  $m/e$  154 ( $[M - 60]^+$ );  $[\alpha]_D +58.2^\circ$  ( $CHCl_3$ );  $\nu_{max}$  ( $CHCl_3$ ) 1 730, 1 640, 1 240, and 1 220  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.32 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 2.02 (3 H, s, OAc), 2.10 (3 H, s, OAc), 4.08 (1 H, m, H-5a), 4.85 (1 H, dd,  $J_{3a,4a}$  6,  $J_{2,3a}$  3 Hz, H-3a), 5.00 (1 H, dd,  $J_{3a,4a}$  6,  $J_{4a,5a}$  8 Hz, H-4a), 5.30 (1 H, m, H-2), and 6.40 (1 H, dd,  $J_{1,2}$  6,  $J_{1,3a}$  2 Hz, H-1).

Methyl 2,3,6-Trideoxy- $\alpha$ -L-erythro-hexopyranoside (Methyl  $\alpha$ -L-Amicetoside) (89).—3,4-Di-O-acetyl-L-rhamnal (87) (5.6 g) was dissolved in dry benzene (100 ml) containing dry methanol (10 ml). Boron trifluoride–ether (1/1) (3.3 ml) was added dropwise and the resulting solution was set

aside at 25 °C for 1 h. The reaction mixture was washed several times with water, and then concentrated to give methyl 4-O-acetyl-2,3,6-trideoxy- $\alpha$ -L-erythro-hex-2-enopyranoside (88) as a colourless oil;  $[\alpha]_D -178.7^\circ$  ( $CH_3OH$ ) {lit.,<sup>46</sup>  $[\alpha]_D -187.0^\circ$  ( $CHCl_3$ )};  $m/e$  155 ( $[M - 31]^+$ );  $\delta_H$  ( $CDCl_3$ ) 1.22 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 2.07 (3 H, s, OAc), 3.42 (3 H, s, 1-OMe), 3.60–4.16 (1 H, m, H-5a), 4.82 (1 H, d,  $J$  2 Hz, H-1e), 5.05 (1 H, dd,  $J_{4a,5a}$  9,  $J_{3,4a}$  2 Hz, H-4a), and 5.80 (2 H, br s, H-2 and H-3). This oil was dissolved in methanol (100 ml) and hydrogenated over 10% palladium-charcoal (2 g) at 25 °C for 16 h, filtered, the filtrate evaporated, and the residue deacetylated with concentrated ammonium hydroxide in methanol. After 16 h at 25 °C the solution was concentrated and chromatography of the residue on a silica gel column ( $110 \times 3$  cm) [acetone–hexane (5 : 95) as eluant] gave methyl 2,3,6-trideoxy- $\alpha$ -L-erythro-hexopyranoside (89) (2.19 g, 57%) as a colourless oil (Found: C, 57.16; H, 9.52.  $C_7H_{14}O_3$  requires C, 57.51; H, 9.65%);  $m/e$  115 ( $[M^+ - 31]^+$ );  $[\alpha]_D -140.7^\circ$  ( $H_2O$ ) {lit.,<sup>48</sup>  $[\alpha]_D -144.0^\circ$  ( $CHCl_3$ )};  $^1H$  n.m.r., and i.r. spectra and the b.p. were identical with those reported.<sup>48</sup>

Methyl 2,3,6-Trideoxy- $\alpha$ -L-glycero-hexopyran-4-uloside (Methyl  $\alpha$ -L-Cineruloside) (90).—Ruthenium dioxide dihydrate (700 mg) was added to a solution of sodium metaperiodate (8.7 g) in water (80 ml). After stirring vigorously for 10 min, the mixture was extracted with distilled carbon tetrachloride ( $2 \times 25$  ml), and the extract was added slowly to a solution of methyl 2,3,6-trideoxy- $\alpha$ -L-erythro-hexopyranoside (89) (300 mg) in distilled carbon tetrachloride (50 ml) at 0 °C. After 10 min, excess of reagent was quenched with isopropanol and the mixture was filtered. The filtrate was concentrated to a small volume and preparative t.l.c. on silica gel plates [acetone–hexane (1 : 4) as eluant] gave methyl 2,3,6-trideoxy- $\alpha$ -L-glycero-hexopyran-4-uloside (90) (150 mg, 50%) as a colourless oil [Found:  $m/e$  144.077 2 ( $M^{+}$ ).  $C_7H_{12}O_3$  requires  $M$ , 144.078 6];  $[\alpha]_D -305.4^\circ$  ( $CHCl_3$ );  $\nu_{max}$  (film) 1 750  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.25 (3 H, d,  $J_{5a,6}$  6.5 Hz, 6-Me), 1.85–2.55 (4 H, m, H-2a, H-2e, H-3a, and H-3e), 3.40 (3 H, s, 1-OMe), 4.18 (1 H, q,  $J_{5a,6}$  6.5 Hz, H-5a), and 4.82 (1 H, dd,  $J_{1e,2e} = J_{1e,2a} = 4$  Hz, H-1e).

1,5-Anhydro-2,3,6-trideoxy-L-erythro-hexitol (91).—3,4-Di-O-acetyl-L-rhamnal (87) (12.0 g) was dissolved in dry benzene (200 ml) containing dry methanol (22 ml). Boron trifluoride–ether (1/1) (7.6 ml) was added dropwise and the resulting solution was maintained at 25 °C for 1 h. The reaction mixture was washed several times with water, then concentrated to leave a clear oil which was dissolved in dry dioxan (250 ml) and added slowly to a suspension of lithium aluminium hydride (10 g) in dioxan (250 ml). The mixture was refluxed for 1 h then set aside at 25 °C for 16 h. Excess of hydride was quenched with water and ethyl acetate, the solution was filtered, the filtrate evaporated, and the residue was hydrogenated over 10% palladium-charcoal (3.7 g) in methanol (200 ml) at 25 °C for 16 h. After filtration and evaporation, chromatography of the residue on a silica gel column ( $110 \times 3$  cm) [diethyl ether–dichloromethane (5 : 95) as eluant] gave 1,5-anhydro-2,3,6-trideoxy-L-erythro-hexitol (91) (2.45 g, 37%) as a colourless oil [Found:  $m/e$  116.083 7 ( $M^{+}$ ).  $C_6H_{12}O_2$  requires  $M$  116.083 7];  $[\alpha]_D -22.0^\circ$  ( $CHCl_3$ );  $\nu_{max}$  ( $CHCl_3$ ) 3 625, 3 450, 3 010, 2 940, and 2 850  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.28 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.43–2.20 (5 H, m, H-2a, H-2e, H-3a, H-3e, and OH), 3.00–3.55 (3 H, m, H-1a, H-1e, and H-5a), and 3.75–4.03 (1 H, m, H-4a).

1,5-Anhydro-2,3,6-trideoxy-L-glycero-hexitol-4-ulose (92).—Ruthenium dioxide dihydrate (900 mg) was added to a solution of sodium metaperiodate (10 g) in water (100 ml). After stirring vigorously for 10 min, the mixture was extracted with distilled carbon tetrachloride (2 × 25 ml), and the extract was added slowly to a solution of 1,5-anhydro-2,3,6-trideoxy-L-erythro-hexitol (91) (300 mg) in distilled carbon tetrachloride (50 ml) at 0 °C. After 10 min, excess of reagent was quenched with isopropanol, the mixture was filtered, and the filtrate concentrated to a small volume. Preparative t.l.c. on silica gel plates [acetone-hexane (1:4) as eluant] then gave 1,5-anhydro-2,3,6-trideoxy-L-glycero-hexitol-4-ulose (92) (80 mg, 27%) as a colourless oil [Found:  $m/e$  114.0671 ( $M^+$ ).  $C_6H_{10}O_2$  requires  $M$ , 114.0680];  $[\alpha]_D -45.4^\circ$  ( $CHCl_3$ );  $\nu_{max}$  (film) 1740  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ), 1.28 (3 H, d,  $J_{5a,6}$  6.5 Hz, 6-Me), 1.85–2.25 (2 H, m, H-2a and H-2e), 2.30–2.60 (2 H, m, H-3a and H-3e), 3.50–4.15 (2 H, m, H-1a and H-1e), and 3.90 (1 H, q,  $J_{5a,6}$  6.5 Hz, H-5a).

Methyl 2-(Acetoxymercurio)-3,4-di-O-acetyl-2,6-dideoxy- $\beta$ -L-gluco-hexopyranoside (96) and Methyl 2-(Acetoxymercurio)-3,4-di-O-acetyl-2,6-dideoxy- $\alpha$ -L-manno-hexopyranoside (95).—3,4-Di-O-acetyl-L-rhamnal (87) <sup>44,45</sup> (8.85 g) dissolved in dry methanol (70 ml) was added dropwise to a suspension of mercuric acetate (13.84 g) in dry methanol (150 ml). The mixture was set aside at 25 °C for 2 h, and then stored in the refrigerator overnight. The solvent was evaporated off, the residue was dissolved in hot methanol (20 ml), and then boiling isopropyl ether (150 ml) was added. The solution was allowed to cool to 25 °C and then refrigerated for 3 h. The liquid was decanted off and the solid washed with cold isopropyl ether, then dried *in vacuo* to give methyl 2-(acetoxymercurio)-3,4-di-O-acetyl-2,6-dideoxy- $\beta$ -L-gluco-hexopyranoside (96) <sup>52</sup> (7.6 g, 36%) as colourless crystals;  $\nu_{max}$  (KBr) 1740 and 1600  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.21 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 2.02 (3 H, s, OAc), 2.05 (3 H, s, OAc), 2.07 (3 H, s, OAc), 2.53 (1 H, dd,  $J_{1a,2a}$  10,  $J_{2a,3a}$  11.5 Hz, H-2a), 3.50 (3 H, s, 1-OMe), 4.53 (1 H, d,  $J_{1a,2a}$  10 Hz, H-1a), 4.63 (1 H, dd,  $J_{3a,4a} = J_{4a,5a} = 9$  Hz, H-4a), and 5.05 (1 H, dd,  $J_{2a,3a}$  11.5,  $J_{3a,4a}$  9 Hz, H-3a). The decanted solution was combined with the isopropyl ether washes and concentrated to give methyl 2-(acetoxymercurio)-3,4-di-O-acetyl-2,6-dideoxy- $\alpha$ -L-manno-hexopyranoside (95) <sup>52</sup> (12.65 g, 61%) as a yellow gum;  $[\alpha]_D +13.5^\circ$  ( $CH_3OH$ );  $\nu_{max}$  (film) 1740 and 1600  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.22 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 2.08 (3 H, s, OAc), 2.09 (3 H, s, OAc), 2.12 (3 H, s, OAc), 3.36 (3 H, s, 1-OMe), 4.72 (1 H, dd,  $J_{3a,4a} = J_{4a,5a} = 9$  Hz, H-4a), 4.97 (1 H, br s, H-1e), and 5.54 (1 H, dd,  $J_{2e,3a}$  5.25,  $J_{3a,4a}$  9 Hz, H-3a).

Methyl 3,4-Di-O-acetyl-2,6-dideoxy- $\alpha$ -L-arabino-hexopyranoside (97).—Methyl 2-(acetoxymercurio)-3,4-di-O-acetyl-2,6-dideoxy- $\alpha$ -L-manno-hexopyranoside (95) <sup>52</sup> (12 g) was dissolved in dry methanol (200 ml), cooled to 0 °C, and sodium borohydride (1.25 g) was added slowly in portions. After 30 min at 0 °C, the solution was filtered and silica gel added to the filtrate. The solvent was evaporated off and the resulting gel was added to a silica gel column and eluted with ethyl acetate-hexane (5:95) to give methyl 3,4-di-O-acetyl-2,6-dideoxy- $\alpha$ -L-arabino-hexopyranoside (97) <sup>52</sup> (3.55 g, 61%) as a colourless oil, b.p. 100 °C at 0.1 mmHg (Found: C, 53.63; H, 7.44.  $C_{11}H_{18}O_6$  requires C, 53.65; H, 7.37%);  $[\alpha]_D -156.1^\circ$  ( $CHCl_3$ );  $\nu_{max}$  (film) 1740  $cm^{-1}$ ;  $m/e$  245 ( $[M - 1]^+$ );  $\delta_H$  ( $CDCl_3$ ) 1.19 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.98 (3 H, s, OAc), 2.04 (3 H, s, OAc), 3.32 (3 H, s, 1-OMe), 4.73 (1 H, dd,  $J_{3a,4a} = J_{4a,5a} = 9.5$  Hz,

H-4a), 4.75 (1 H, br s, H-1e), and 5.27 (1 H, ddd,  $J_{2a,3a}$  11,  $J_{3a,4a}$  9.5, and  $J_{2e,3a}$  5.5 Hz, H-3a).

Methyl 2,6-Dideoxy-3-O-*p*-toluenesulphonyl- $\alpha$ -L-arabino-hexopyranoside (99).—Methyl 3,4-di-O-acetyl-2,6-dideoxy- $\alpha$ -L-arabino-hexopyranoside (97) <sup>52</sup> (3.50 g) was dissolved in dry methanol (100 ml) and sodium methoxide (1.42 g) was added. After 0.5 h, the solution was concentrated and the residue chromatographed on a silica gel column (3 × 30 cm) [methanol-chloroform (5:95) as eluant] to give methyl 2,6-dideoxy- $\alpha$ -L-arabino-hexopyranoside (98) <sup>52-55</sup> (2.3 g, 99%) as a colourless oil;  $[\alpha]_D -129.0^\circ$  ( $CHCl_3$ );  $m/e$  [ $M - 31$ ]<sup>+</sup>;  $\delta_H$  ( $CDCl_3$ ) 1.34 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 3.38 (3 H, s, 1-OMe), and 4.72 (1 H, dd,  $J_{1e,2a}$  3,  $J_{1e,2e}$  1 Hz, H-1e). To a solution of this diol (98) (2.25 g) in dry pyridine (75 ml) at 0 °C was added *p*-toluenesulphonyl chloride (2.70 g) (freshly recrystallized). After 6 d at 7 °C, the reaction mixture was poured into ice-water and extracted several times with chloroform. The combined organic fractions were washed with dilute hydrochloric acid and water, dried ( $MgSO_4$ ) and concentrated. Chromatography on a silica gel column (3 × 30 cm) (chloroform as eluant) gave methyl 2,6-dideoxy-3-O-*p*-toluenesulphonyl- $\alpha$ -L-arabino-hexopyranoside (99) <sup>56</sup> (2.6 g, 50%) as a colourless oil;  $[\alpha]_D -101.7^\circ$  ( $CHCl_3$ );  $m/e$  285 [ $M - 31$ ]<sup>+</sup>;  $\nu_{max}$  (film) 1360 and 1180  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 1.32 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 2.47 (3 H, d, ArMe), 3.30 (3 H, s, 1-OMe), 4.65 (1 H, dd,  $J_{1e,2a}$  3,  $J_{1e,2e}$  1 Hz, H-1e), 7.27 (2 H, m, Ar), and 7.97 (2 H, m, Ar).

Methyl 2,3,6-Trideoxy-3-dimethylamino- $\alpha$ -L-ribo-hexopyranoside (Methyl  $\alpha$ -L-Megosaminide) (37).—A solution of methyl 2,6-dideoxy-3-O-*p*-toluenesulphonyl- $\alpha$ -L-arabino-hexopyranoside (99) (3.5 g) and sodium azide (6.2 g) dissolved in DMF (30 ml) and water (5 ml) was heated to 100 °C for 16 h. The mixture was concentrated to a gum, and the residue dissolved in chloroform and washed several times with water. The organic fraction was dried and concentrated, and the residue chromatographed on a silica gel column (2.5 × 150 cm) (chloroform as eluant). All the azide-containing fractions were combined and hydrogenated over 10% palladium-charcoal (300 mg) in a solution of methanol containing formaldehyde (40%, 2 ml) for 16 h at 25 °C. The mixture was filtered, the filtrate concentrated, and the residue chromatographed on a silica gel column (2.0 × 150 cm) [methanol-chloroform (7:93) as eluant] to give methyl 2,3,6-trideoxy-3-dimethylamino- $\alpha$ -L-ribo-hexopyranoside (37) (133 mg, 6%) as a yellow oil;  $[\alpha]_D -38.4^\circ$  ( $CH_3OH$ ) [lit.,<sup>9</sup>  $[\alpha]_D -58.8^\circ$  ( $CH_3OH$ ), distilled sample]; <sup>1</sup>H and <sup>13</sup>C n.m.r. and i.r. spectra were identical with those of the natural material.

Methyl 3,4-Di-O-acetyl-2,6-dideoxy- $\beta$ -L-arabino-hexopyranoside (101).—Methyl 2-(acetoxymercurio)-3,4-di-O-acetyl-2,6-dideoxy- $\beta$ -L-gluco-hexopyranoside (96) <sup>52</sup> (7.5 g) was dissolved in dry methanol (150 ml), cooled to 0 °C, and sodium borohydride (750 mg) was added slowly in portions. After 30 min at 0 °C, the solution was filtered and silica gel added to the filtrate. The solvent was evaporated off and the resulting gel was added to a silica gel column and eluted with ethyl acetate-hexane (1:9) to give methyl 3,4-di-O-acetyl-2,6-dideoxy- $\beta$ -L-arabino-hexopyranoside (101) <sup>52</sup> (2.0 g, 55%) as a colourless oil, b.p. 100 °C at 0.1 mmHg (Found: C, 53.51; H, 7.40.  $C_{11}H_{18}O_6$  requires C, 53.65; H, 7.37%);  $[\alpha]_D +13.1^\circ$  ( $CHCl_3$ );  $\nu_{max}$  (film) 1740  $cm^{-1}$ ;  $m/e$  245 ( $[M - 1]^+$ );  $\delta_H$  ( $CDCl_3$ ) 1.23 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 2.01 (3 H, s, OAc), 2.04 (3 H, s, OAc), 3.48 (3 H, s, 1-OMe), 4.43 (1 H, dd,  $J_{1a,2a}$  9.5,  $J_{1a,2e}$  2 Hz, H-1a), 4.70

(1 H, dd,  $J_{3a,4a} = J_{4a,5a} = 9$  Hz, H-4a), and 4.98 (1 H, ddd,  $J_{2a,3a} 11$ ,  $J_{3a,4a} 9$ ,  $J_{2e,3a} 5$  Hz, H-3a).

**Methyl 2,6-Dideoxy-3-O-*p*-toluenesulphonyl- $\beta$ -L-arabino-hexopyranoside (103).**—Methyl 3,4-di-*O*-acetyl-2,6-dideoxy- $\beta$ -L-arabino-hexopyranoside (101)<sup>52</sup> (1.7 g) was dissolved in dry methanol (40 ml) and sodium methoxide (746 mg) was added. After 1.5 h the solution was concentrated and the residue chromatographed on a silica gel column (3  $\times$  30 cm) [methanol-chloroform (5 : 95) as eluant] to give methyl 2,6-dideoxy- $\beta$ -L-arabino-hexopyranoside (102)<sup>52-55</sup> (1.1 g, 98%) as a colourless oil;  $[\alpha]_D^{25} + 63.0^\circ$  (CH<sub>3</sub>OH);  $m/e$  131  $M^-$   $-31^+$ ;  $\delta_H$  (CDCl<sub>3</sub>) 1.35 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 3.50 (3 H, s, 1-OMe), and 4.38 (1 H, dd,  $J_{1a,2a}$  9.5,  $J_{1a,2e}$  2 Hz, H-1a). To a solution of this diol (102) (1.1 g) in dry pyridine (35 ml) at 0 °C was added *p*-toluenesulphonyl chloride (1.35 g) (freshly recrystallized). After 5 d at 7 °C, the reaction mixture was poured into ice-water and extracted several times with chloroform, and the combined organic extracts were washed with water and dilute hydrochloric acid, dried (MgSO<sub>4</sub>), and concentrated. Chromatography of the residue on a silica gel column (3  $\times$  30 cm) (chloroform as eluant) gave methyl 2,6-dideoxy-3-*O*-*p*-toluenesulphonyl- $\beta$ -L-arabino-hexopyranoside (103)<sup>54</sup> (830 mg, 39%) as a colourless oil (Found: C, 51.35; H, 6.25, S, 9.70. C<sub>14</sub>H<sub>20</sub>O<sub>6</sub>S $\cdot$ 0.5H<sub>2</sub>O requires C, 51.67; H, 6.51; S, 9.86%);  $[\alpha]_D^{25} + 11.6^\circ$  (CHCl<sub>3</sub>);  $\nu_{max}$  (film) 1 360, and 1 180 cm<sup>-1</sup>;  $\delta_H$  (CDCl<sub>3</sub>) 1.37 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 2.48 (3 H, s, Ar-Me), 3.50 (3 H, s, 1-OMe), 4.32 (1 H, dd,  $J_{1a,2a}$  9.5,  $J_{1a,2e}$  2 Hz, H-1a), 7.32 (2 H, m, Ar), and 8.00 (2 H, m, Ar).

**Methyl 3-Azido-2,3,6-trideoxy- $\beta$ -L-ribo-hexopyranoside (104).**—Methyl 2,6-dideoxy-3-*O*-*p*-toluenesulphonyl- $\beta$ -L-arabino-hexopyranoside (103) (780 mg) was dissolved in DMF (20 ml) and sodium azide (351 mg) was added along with enough water to dissolve it completely. The mixture was heated at 120 °C for 16 h and then concentrated. The residue was diluted with ethyl acetate and washed several times with water, and the organic fraction was dried and concentrated to leave a yellow oil, chromatography of which on a silica gel column (2.5  $\times$  15 cm) (chloroform as eluant) gave methyl 3-azido-2,3,6-trideoxy- $\beta$ -L-ribo-hexopyranoside (104)<sup>54,57</sup> (240 mg, 52%) as a colourless oil (Found:  $m/e$  156.076 9 [ $M^-$  - OMe]<sup>+</sup>. C<sub>8</sub>H<sub>10</sub>N<sub>3</sub>O<sub>2</sub> requires  $M^-$  - OMe, 156.078 6);  $[\alpha]_D^{25} - 29.7^\circ$  (CHCl<sub>3</sub>);  $\nu_{max}$  (film) 2 100 cm<sup>-1</sup>;  $\delta_H$  (CDCl<sub>3</sub>) 1.33<sup>3</sup> (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.67 (1 H, m, OH), 1.82 (1 H, ddd,  $J_{2a,2e}$  14,  $J_{1a,2a}$  9,  $J_{2a,3e}$  3.5 Hz, H-2a), 2.20 (1 H, ddd,  $J_{2e,2a}$  14,  $J_{2e,3e}$  4,  $J_{1a,2e}$  2.5 Hz, H-2e), 3.50 (3 H, s, 1-OMe) 3.91 (1 H, dq,  $J_{4a,5a}$  9,  $J_{5a,6}$  6 Hz, H-5a), and 4.67 (1 H, dd,  $J_{1a,2a}$  9,  $J_{1a,2e}$  2.5 Hz, H-1a).

**Methyl 2,3,6-Trideoxy-3-dimethylamino- $\beta$ -L-ribo-hexopyranoside (Methyl  $\beta$ -L-Megosaminide) (38).**—A solution of methyl 3-azido-2,3,6-trideoxy- $\beta$ -L-ribo-hexopyranoside (104) (160 mg) in methanol (30 ml) containing formaldehyde solution (40%, 0.7 ml) was hydrogenated over 10% palladium-charcoal (100 mg) for 18 h at 55 lb in<sup>-2</sup>. The mixture was filtered and the filtrate concentrated to leave a yellow gum, chromatography of which on a silica gel column (2.5  $\times$  15 cm) [methanol-chloroform (5 : 95) as eluant] gave methyl 2,3,6-trideoxy-3-dimethylamino- $\beta$ -L-ribo-hexopyranoside (38) (75 mg, 46%) as a colourless oil;  $[\alpha]_D^{25} + 116.3^\circ$  (CH<sub>3</sub>OH) [lit.,<sup>9</sup>  $[\alpha]_D^{25} + 119.1^\circ$  (CH<sub>3</sub>OH), distilled sample]; <sup>1</sup>H and <sup>13</sup>C n.m.r. and i.r. spectra were identical with the natural material.

**Methyl 4-*O*-Benzoyl-6-bromo-2,6-dideoxy-3-*O*-methanesulphonyl- $\alpha$ -D-arabino-hexopyranoside (29).**—A mixture of

the known methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methanesulphonyl- $\alpha$ -D-arabino-hexopyranoside (28)<sup>58</sup> (4 g), barium carbonate (8 g), and *N*-bromosuccinimide (2.7 g) in anhydrous carbon tetrachloride (175 ml) was stirred under reflux for 3 h. The mixture was filtered, the precipitate was washed with dichloromethane, the combined filtrates were evaporated to dryness, and the residue was partitioned between water and dichloromethane. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness to give methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*O*-methanesulphonyl- $\alpha$ -D-arabino-hexopyranoside (29) (4.5 g, 91%) as an oil;  $\delta_H$  (CDCl<sub>3</sub>) 2.00–2.76 (2 H, m, H-2a and H-2e), 2.83 (3 H, s, MeSO<sub>2</sub>), 3.45 (3 H, s, 1-OMe), 3.80–4.30 (1 H, m, H-5a), 4.94 (1 H, dd,  $J_{1e,2e}$  1,  $J_{1e,2a}$  3 Hz, H-1e), 5.06–5.40 (2 H, m, H-3a and H-4a), 7.60 (3 H, m, Ar), and 8.10 (2 H, m, Ar).

**Methyl 4-*O*-Benzoyl-2,6-dideoxy-3-*O*-methanesulphonyl- $\alpha$ -D-arabino-hexopyranoside (30).**—A mixture of methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*O*-methanesulphonyl- $\alpha$ -D-arabino-hexopyranoside (29) (5.4 g), barium carbonate (5 g), and 10% palladium-charcoal (5 g) in methanol (200 ml) was hydrogenated for 24 h. The solution was filtered and evaporated, and the resulting syrup was dissolved in dichloromethane, washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated to give methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-methanesulphonyl- $\alpha$ -D-arabino-hexopyranoside (30) (3.2 g, 73%) as an oil;  $\delta_H$  (CDCl<sub>3</sub>) 1.24 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.94–2.60 (2 H, m, H-2a and H-2e), 2.77 (3 H, s, MeSO<sub>2</sub>), 3.33 (3 H, s, 1-OMe), 3.83–4.33 (1 H, m, H-5a), 4.90 (1 H, dd,  $J_{1e,2e}$  1,  $J_{1e,2a}$  3 Hz, H-1e) 5.00–5.24 (2 H, m, H-3a and H-4a), 7.60 (3 H, m, Ar), and 8.10, (2 H, m, Ar).

**Methyl 3-Azido-4-*O*-benzoyl-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranoside (31).**—Methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-methanesulphonyl- $\alpha$ -D-arabino-hexopyranoside (30) (3.4 g) and sodium azide (1.68 g) in anhydrous DMF (120 ml) were heated at 140 °C for 4 d. The solution was filtered, diluted with water, extracted with benzene, and the organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated to dryness. Preparative t.l.c. of the residue on silica gel plates [methanol-chloroform (0.5 : 99.5) as eluant] gave methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranoside (31) (640 mg, 22%) as an oil;  $\delta_H$  (CDCl<sub>3</sub>) 1.25 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 2.13 (2 H, m, H-2a and H-2e), 3.4 (3 H, s, 1-OMe), 4.10–4.50 (2 H, m, H-3e and H-5a), 4.66 (1 H, dd,  $J_{1e,2e} = J_{1e,2a} = 3$  Hz, H-1e), 4.90 (1 H, dd,  $J_{2e,3a}$  4,  $J_{4a,5a}$  10 Hz, H-4a), 7.60 (3 H, m, Ar), and 8.10 (2 H, m, Ar).

**Methyl 3-Azido-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranoside (32).**—A solution of methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranoside (31) (400 mg) in anhydrous methanol (30 ml) containing sodium methoxide (300 mg) was stirred at 25 °C for 24 h. After neutralization with Amberlite MB-3 resin and concentration, dichloromethane was added to the residue. The solution was dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered through a silica gel column to give crystalline methyl 3-azido-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranoside (32) (250 mg, 97%);  $[\alpha]_D^{25} + 235.0^\circ$  (CHCl<sub>3</sub>,  $c$  1.0);  $\delta_H$  (CDCl<sub>3</sub>) 1.26 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 2.10 (2 H, m, H-2a and H-2e), 3.33 (3 H, s, 1-OMe), 3.66–4.16 (2 H, m, H-3a and H-5a), and 4.60 (1 H, m, H-1e).

**Methyl 3,4,6-Trideoxy-3-dimethylamino- $\alpha$ -D-ribo-hexopyranoside (Methyl  $\alpha$ -D-Megosaminide) (41).**—A mixture of methyl 3-azido-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranoside (32) (200 mg) and 10% palladium-charcoal (100 mg) in methanol (30 ml) containing formaldehyde solution (40%, 1 ml), was hydrogenated for 24 h. The mixture was filtered and

evaporated, and the resulting syrup was dissolved in dichloromethane, washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated to give methyl  $\alpha$ -D-megosaminide (41) (110 mg, 54%) as an oil;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.30 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.57–2.00 (2 H, m, H-2a and H-2e), 2.33 (6 H, s, 3-NMe<sub>2</sub>), 2.33 (1 H, m, H-3a), 3.37 (3 H, s, 1-OMe), 3.62 (1 H, m, H-4e), 3.98 (1 H, m, H-5e), and 4.64 (1 H, dd,  $J_{1a,2e}$  4,  $J_{1a,2a}$  8 Hz, H-1a).

*Methyl 3-Azido-4-O-benzoyl-2,3,6-trideoxy- $\beta$ -D-ribo-hexopyranoside (33).*—A solution of methyl 3-azido-4-O-benzoyl-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranoside (31) (600 mg) in methanol (30 ml) containing 5% hydrogen chloride was refluxed for 2 h. After neutralization with Amberlite IRA-45 resin, the solution was evaporated to dryness, and the residue was extracted with dichloromethane, washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and the organic layer evaporated to give a mixture of methyl 3-azido-4-O-benzoyl-2,3,6-trideoxy- $\beta$ -D-ribo-hexopyranoside (33) and the  $\alpha$ -anomer (31) (7 : 3) (500 mg, 83%) as an oil which could not be chromatographically separated;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.20 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.28 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 3.35 (3 H, s, 1-OMe), and 3.42 (3 H, s, 1-OMe).

*Methyl 3-Azido-2,3,6-trideoxy- $\beta$ -D-ribo-hexopyranoside (34).*—A solution of a mixture of methyl 3-azido-2,3,6-trideoxy- $\beta$ - and - $\alpha$ -D-ribo-hexopyranoside, (33) and (31) (7 : 3) (500 mg) in anhydrous methanol (30 ml) containing sodium methoxide (400 mg) was stirred at 25 °C for 24 h. After neutralization with Amberlite MB-3 resin and concentration, dichloromethane was added to the residue, and the solution dried ( $\text{Na}_2\text{SO}_4$ ), and filtered through a silica gel column to give methyl 3-azido-2,3,6-trideoxy- $\beta$ -D-ribo-hexopyranoside (34) and the  $\alpha$ -anomer (32) (7 : 3) (300 mg, 93%) as an oil that could not be chromatographically separated;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.25 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 1.29 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 3.27 (3 H, s, 1-OMe), and 3.40 (3 H, s, 1-OMe).

*Methyl 2,3,6-Trideoxy-3-dimethylamino- $\beta$ -D-ribo-hexopyranoside (Methyl  $\beta$ -D-Megosaminide) (42).*—A mixture of methyl 3-azido-2,3,6-trideoxy- $\beta$ - and - $\alpha$ -D-ribo-hexopyranoside (34) and (32) (7 : 3) (300 mg) and 10% palladium-charcoal (150 mg) in methanol (40 ml) containing formaldehyde solution (40% 1 ml) was hydrogenated for 24 h. The mixture was filtered and evaporated, and the resulting syrup was dissolved in dichloromethane, washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated to give methyl  $\beta$ -D-megosaminide (42) and the  $\alpha$ -anomer (41) (7 : 3) (280 mg, 92%) as an oil that could not be chromatographically separated;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 2.33 (12 H, s, 3-NMe<sub>2</sub>), 3.37 (3 H, s, 1-OMe), and 3.40 (3 H, s, 1-OMe). The <sup>13</sup>C n.m.r. resonances of (42) and (41) were identical ( $\pm 0.1$  p.p.m.) with those of (38) and (37), respectively.

*Methyl 2,3,6-Trideoxy-3-dimethylamino- $\alpha$ -D-arabino-hexopyranoside (Methyl  $\alpha$ -D-Angolosaminide) (35).*—Methyl 3-azido-2,3,6-trideoxy- $\alpha$ -D-arabino-hexopyranoside (18) (180 mg) and 10% palladium-charcoal (150 mg) in methanol (40 ml) containing formaldehyde solution (40%, 1 ml) was hydrogenated for 17 h. The mixture was filtered and evaporated, and the resulting syrup was dissolved in dichloromethane, washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. Preparative t.l.c. on silica gel [ethyl acetate-dichloromethane (1 : 9) as eluant] gave methyl  $\alpha$ -D-angolosaminide (35) (120 mg, 66%) as an oil;  $[\alpha]_{\text{D}}^{22} + 87.0^\circ$  ( $\text{CH}_3\text{OH}$ ,  $c$  1.8);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.28 (3 H, s,  $J_{5a,6}$  6 Hz, 6-Me), 1.50–2.10 (2 H, m, H-2a and H-2e), 2.23 (6 H, s, 3-NMe<sub>2</sub>),

3.32 (3 H, s, 1-OMe), 2.60–3.80 (3 H, m, H-3a, H-4a, and H-5a), and 4.70 (1 H, dd,  $J_{1e,2e} = J_{1e,2a} = 3$  Hz, H-1e).

*Methyl 2,3,6-Trideoxy-3-dimethylamino- $\beta$ -D-arabino-hexopyranoside (Methyl  $\beta$ -D-Angolosaminide) (36).*—Methyl 3-azido-2,3,6-trideoxy- $\beta$ -D-arabino-hexopyranoside (24) (220 mg) and 10% palladium-charcoal (180 mg) in methanol (45 ml) containing formaldehyde solution (40%, 1 ml), was hydrogenated for 17 h. The mixture was filtered and evaporated, and the residue dissolved in dichloromethane, washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. Preparative t.l.c. of the residue on silica gel gave methyl  $\beta$ -D-angolosaminide (36) (135 mg, 61%) as an oil;  $[\alpha]_{\text{D}}^{22} - 68.0^\circ$  ( $\text{CH}_3\text{OH}$ ,  $c$  1.3);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.33 (3 H, d,  $J_{5a,6}$  6 Hz, 6-Me), 2.20 (6 H, s, 3-NMe<sub>2</sub>), 1.40–2.40 (2 H, m, H-2a and H-2e), 3.42 (3 H, s, 1-OMe), 2.60–3.40 (3 H, m, H-3a, H-4a, and H-5a), and 4.32 (1 H, dd,  $J_{1e,2a}$  2.5,  $J_{1a,2a}$  8.5 Hz, H-1a).

*Crystallographic Study of 4'-O-(4-Iodobenzoyl)-megalomycin A (6).*—Colourless crystals of (6) were grown from acetone-water. A crystal *ca.* 0.15  $\times$  0.08  $\times$  0.09 mm was mounted in a glass capillary tube with epoxy resin, and the space group was found to be  $P2_12_12_1$ , by a combination of film and counter methods. The cell constants were found using 16 reflections on a Syntex  $P2_1$  four-circle diffractometer (Ni-filtered  $\text{Cu-K}\alpha$  radiation,  $\lambda = 1.54178 \text{ \AA}$ ).

*Crystal data.* Crystals are orthorhombic,  $a = 12.699(2)$ ,  $b = 19.501(6)$ ,  $c = 25.741(9) \text{ \AA}$ ;  $U = 6359.52 \text{ \AA}^3$ ,  $D_{\text{m}}$  (floatation in KI) = 1.181(4)  $\text{g cm}^{-3}$ ,  $Z = 4$ ,  $D_{\text{c}} = 1.179 \text{ g cm}^{-3}$ ;  $F(000) = 2380$ ,  $\mu(\text{Cu-K}\alpha) = 11.26 \text{ cm}^{-1}$ . Intensity data were collected using a scintillation counter with pulse-height discrimination, a  $\theta$ – $2\theta$  scan technique, scan rate  $1^\circ \text{ min}^{-1}$ , and four reflections measured in every 100 to monitor the extent of crystal decomposition and movement. The extent of decomposition after 8 d of data collection was 35%. Of 3762 reflections with  $\theta < 50^\circ$ , 1812 with  $I \geq 2.5 \sigma(I)$  were considered observed. All data were corrected for Lorentz, polarization, decomposition, and absorption.

The structure was solved by the heavy-atom technique. A Patterson calculation revealed the position of the unique I atom in the unit cell. Its position was used in a Fourier calculation which revealed the position of 12 other atoms. Inclusion of these additional atoms in a second Fourier calculation led to the position of all but two of the remaining atoms, and a difference-Fourier revealed the positions of these two carbon atoms. Block-diagonal least-squares refinement, initially isotropic with unit weights, and then anisotropic using weight  $w = 1/\sigma^2$  gave a final  $R$  of 0.0949 and  $R' \{ = [(\sum w|F_o| - |F_c|)^2 / \sum w F_o^2]^{1/2} \}$  of 0.1029. Fractional co-ordinates are given in Table 2, and bond distances and angles in Tables 3 and 4, respectively.\* Anisotropic thermal parameters and observed and calculated structure factors are deposited in Supplementary Publication No. SUP 22453 (25 pp.).†

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\* The fractional co-ordinates of the terminal carbon atom, C(7''), presented a serious problem in the structure determination. C(7'') exhibits large anisotropic thermal vibrations leading to a high standard deviation in its position and, consequently, unreliable bond distances and angles.

† For details see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue.



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