Synthesis of New Pseudodisaccharide Aminoglycoside Antibiotics from Carbohydrates†

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(Received for publication March 2, 1995)

Novel pseudodisaccharide-type aminocyclitol antibiotic models, built up from D-arabinose, D-ribose, D-glucosamine, L-ristosamine and L-acosamine have been synthesized by the glycosylation of suitably protected (azido)deoxyinososе aglycones derived by the Ferrier carbocyclic ring transformation of carbohydrate precursors. An alternative approach to related pseudodisaccharides, based on the Ferrier carbocyclization of reducing disaccharides, has also been elaborated. This latter method extends the scope of the Ferrier reaction, by demonstrating that acid-labile 2-deoxydisaccharides can also be readily transformed into the corresponding pseudodisaccharides under the slightly acidic conditions of this ring-transformation.

Various synthetic routes have been developed for the production of the carbasugar analogues (pseudomonosaccharides)[1,2] of deoxy and aminodeoxy monosaccharides. Less attention, however, has been focussed on the synthesis of related amino monocarbadisaccharides (pseudodisaccharides). It is although numerous pseudodisaccharide-type aminocyclitol antibiotics (*i.e.* fortimycins, sporaricins, sannamycins, istamycins, *etc.*) have been shown[3] to possess significant antibacterial activity, structurally similar compounds have been found to be glycosidase enzyme inhibitors[2], and most recently certain (amino)glycosylinositol phosphates are considered[4] as insulin mimetics.

For the chemical synthesis of related pseudodisaccharides direct glycosylation[5~7] of a suitably protected cyclitol, Ferrier carbocyclic ring-transformation[8] of disaccharides[9~12] or the cycloaddition[13] of maleic anhydride on a dienyl glycoside have been employed. However, except for a very recent approach to sannamycin analogues,[14] neither of these methods has been applied so far for the synthesis of pseudodisaccharide-type aminocyclitol antibiotics carrying a 2-deoxy sugar portion and an azido or amino function in the cyclitol (aglycone) moiety. The present paper reports on the preparation of novel pseudodisaccharide aminoglycoside antibiotics built up from naturally occurring sugars, including pentofuranose (D-ribose, D-arabinose), D-glucosamine and 3-amino-2,3,6-trideoxy-L-hexose[15] components, by using[16] direct glycosylation, or the Ferrier ring-transformation of a reducing disaccharide.

Results and Discussion

The deoxyinososes (2*S*,3*R*,5*R*)-2,3-dibenzoyloxy-5-hydroxycyclohexanone (**1**) and (2*S*,3*R*,5*R*)-3-azido-2-benzoyloxy-5-hydroxycyclohexanone (**2**) were obtained by the Ferrier carbocyclic ring-transformation of the corresponding methyl trideoxy-hex-5-enopyranosides as previously reported[17,18]. For the preparation of the 2-*O*-benzyl analogue (**3**) of **2**, with an ether group instead of the more labile ester at *O*-2, methyl 3-azido-6-bromo-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside (**5**) was synthesized from the known[19,20] 4-*O*-benzoate **4**. Thus, *O*-4 deacylation of **4** under Zemplén conditions afforded **5** in a quantitative yield. Simultaneous 4-*O*-benzylation and C-5 dehydrobromination of **5** could be readily effected in a one-pot operation by treatment with benzyl bromide and sodium hydride in anhydrous *N*,*N*-dimethylformamide to afford 88% of the *exo*-methylene sugar **6**. Then Ferrier carbocyclization of **6** was executed with a catalytic amount of mercuric trifluoroacetate in aqueous acetone, giving rise to a *ca.* 9:1 mixture of (2*S*,3*R*,5*R*)-3-azido-2-benzyloxy-5-hydroxycyclohexanone (**3**) and its (2*S*,3*R*,5*S*)-isomer, form which the desired pure **3** was isolated by means of column chromatography.

When the cyclitol aglycones **1~3** were subjected to glycosylation with different glycosyl donors under various conditions extensive β-elimination of the C-5 hydroxyl group occurred, and the formation of complex mixtures was detected. At the same time, no elimination was observed upon the *p*-toluenesulfonic acid-catalyzed

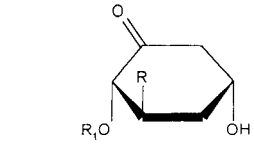
† For a preliminary account see Ref. 16.
Dedicated to the 60th birthday of Professor S. Ōmura.

reaction of **2** with 3,4-dihydro-2*H*-pyran, resulting in the diastereoisomeric dihydropyranyl "model glycosides" **7**. However, no related pseudodisaccharide could be obtained by the analogous reaction of **2** with hex-1-enitols: 3,4,6-tri-*O*-benzyl-D-glucal failed to react and 3,4,6-tri-*O*-acetyl-D-glucal suffered decomposition.

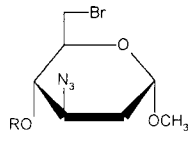
These experiences necessitated the protection of the carbonyl function preceding glycosylation. Thus, compounds **1**~**3** were treated with 1,2-ethanedithiol in the presence of boron trifluoride etherate to give the dithiolane derivatives **9**~**11**, respectively, with good yield. The azidocyclohexanone **2** was also converted into the *O*-benzyloxime **12**.

Glycosylation of the protected deoxyinososes **9**, **10** and **12** with 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide[21] under Helferich conditions readily afforded the α-ribofuranosyl pseudodisaccharides **13**, **14** and **16**, respectively, over 75% yield. The trimethylsilyl triflate promoted coupling of **10** with 2,3-*O*-isopropylidene-1,5-di-*O*-(*p*-nitrobenzoyl)-α,β-D-ribofuranose[22] and 2-deoxy-2-phthalimido-1,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranose[23] proceeded with modest yields, giving rise to the protected α-ribofuranosyl (**22**) and α-glucosaminyl (**24**) pseudodisaccharides. Analogous glycosylation of

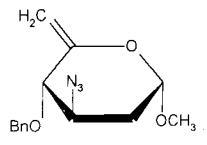
Fig. 1. The structure of the cyclitol aglycones **9**~**12** and of the intermediates of their syntheses.



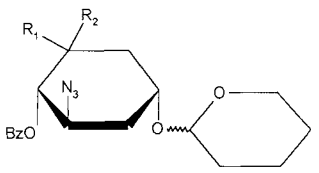
1 R=OBz; R_1=Bz
2 R=N_3; R_1=Bz
3 R=N_3; R_1=Bn



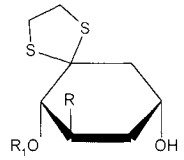
4 R=Bz
5 R=H



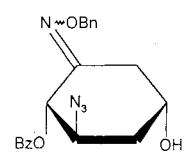
6



7 R_1R_2=O
8 R_1R_2=$S(CH_2)_2S$

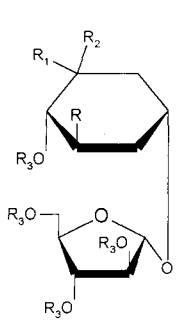


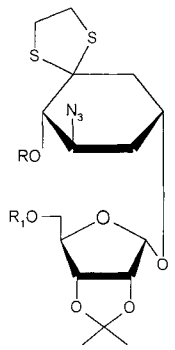
9 R=OBz; R_1=Bz
10 R=N_3; R_1=Bz
11 R=N_3; R_1=Bn

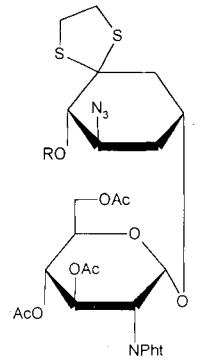


12

Fig. 2. The synthesized pentofuranosyl and glucosaminyl pseudodisaccharides **13**~**25**.





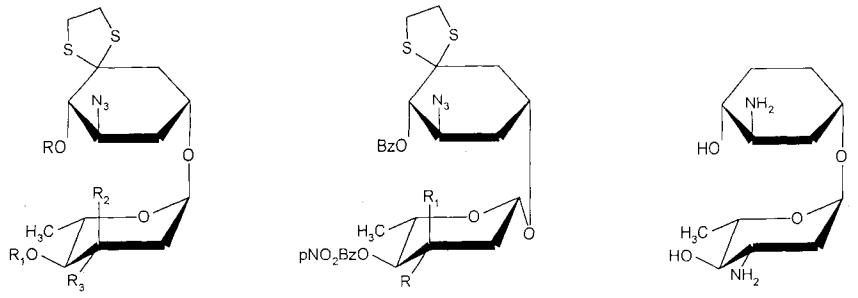


13 R=OBz; R_1,R_2=$S(CH_2)_2S$; R_3=Bz
14 R=N_3; R_1,R_2=$S(CH_2)_2S$; R_3=Bz
15 R=N_3; R_1,R_2=$S(CH_2)_2S$; R_3=H
16 R=N_3; R_1,R_2=NOBn; R_3=Bz
17 R=N_3; R_1,R_2=NOBn; R_3=H
18 R=NH_2; R_1=R_2=R_3=H
19 R=OH; R_1=R_2=R_3=H
20 R=R_2=$NHCOCF_3$; R_1=R_3=H
21 R=R_1=$NHCOCF_3$; R_2=R_3=H

22 R=Bz; R_1=pNO_2Bz
23 R=R_1=H

24 R=Bz
25 R=Bn

Fig. 3. The aminocyclitol antibiotic models **26**~**31** carrying azide(amino)-trideoxyhexopyranose moieties.



26 R=Bz; R_1=pNO_2Bz; R_2=H; R_3=N_3

27 R=Bz; R_1=pNO_2Bz; R_2=N_3; R_3=H

28 R=R_1=R_2=H; R_3=N_3

29 R=N_3; R_1=H

30 R=H; R_1=N_3

31

the acceptor **11** with the above glucosaminyl donor gave 28% of the 2-*O*-benzyl analogue **25** of **24**, and formation of the corresponding β-anomer could not be detected in either of the cases.

The trimethysilyl triflate-catalyzed glycosylation was most particularly useful for synthesizing novel pseudodisaccharide-type aminocyclitol antibiotic models carrying a 3-azido(amino)-2,3,6-trideoxy-L-hexose as the carbohydrate portion. Thus, coupling the azidoinosose acceptor **10** with 3-azido-1,4-di-*O*-(*p*-nitrobenzoyl)-2,3,6-trideoxy-L-*arabino*[24] and *ribo*-hexopyranose[24] furnished *ca.* 10:1 mixtures of the α- (**26** and **27**) and β-pseudodisaccharides (**29** and **30**) in high yields, and except **30** all of the new glycosides could be readily isolated upon column chromatographic separation.

Proof for that glycosylation occurred in each case at the C-5 hydroxyl group of the aglycones **9**~**12** was obtained from the ^{13}C NMR downfield glycosidation shift values (Δ 3.5~12 ppm; see Table 1).

The α-anomeric configuration of the pentofuranosyl glycosides **13**, **14**, **16** and **22** was clearly demonstrated by the observed ^{13}C NMR chemical shift values (Table 1) for the anomeric (C-1′) carbon (104.62, 104.04, 104.07 and 107.21 ppm, respectively) characteristic of the α-glycosides of arabino- and ribofuranose. The C-1′ carbon of the glucosamine portion of **24** and **25** resonated at δ 94.89 and 95.48 ppm, respectively, and the same carbon of the 3-azido-trideoxyhexopyranosyl moiety of **26** and **27** appeared at δ 95.36 and 96.00 ppm, each peculiar to an α-glycosidic linkage of hexopyranosides. For the β-glycoside **29** carbon C-1′ was assigned at δ 97.84 ppm.

The ^1H NMR spectral data (Table 2) further supported the α-glycosidic structure of compounds **24**~**27**. The anomeric proton (H-1′) of these glycosides was assigned at δ 4.32 ppm ($J_{1,2}$=3.5 Hz), δ 4.20 ppm ($J_{1,2}$=2.5 Hz), δ 5.24 ppm ($J_{1',2'a}$=3.5 Hz; $J_{1',2'e}$=1.5 Hz) and δ 5.04 ppm ($J_{1',2'a}$=3.5 Hz; $J_{1',2'e}$=2.0 Hz), respectively. For the single β-anomer, isolated, the values $\delta_{H\text{-}1'}$ 4.98 ppm ($J_{1',2'a}$=9.5 Hz; $J_{1',2'e}$=2.5 Hz) were observed.

Attempted removal of the dithioacetal protecting group of the synthesized dithiolane-pseudodisaccharides, in order to regenerate the carbonyl function, failed under each of the employed reaction conditions (in the presence of mercuric salts, with phosphorous tetraiodide[25] or *N*-bromosuccinimide in aqueous acetonitrile[26] and by means of transthioacetalization[27] with 4-nitrobenzaldehyde). Although reaction of the tetrahydropyranyl "model-glycoside" **8** with phenyl dichlorophosphate in the presence of sodium iodide and DMF[28] resulted in the liberation of the carbonyl group, thus affording **7** in satisfactory (66%) yield, this method could not be successfully extended to the protected pseudodisaccharides carrying pentofuranose or hexopyranose moieties.

By the reduction of the prepared cyclitol-glycosides **13**, **14**, **16** and **26** the target new pseudodisaccharide-type aminocyclitol antibiotics **18**~**21** and **31** were synthesized. Zemplén *O*-deacylation of **13**, followed by desulfurization with Raney nickel gave the 1,2,4-trihydroxycyclohexane glycoside **19**, and the respective 2-amino-1,4-dihydroxy analogue **18** was obtained from **14** upon similar *O*-deacylation (**14**→**15**) and subsequent hydrogenation. Catalytic hydrogenation of the benzyloximino compound **17**, prepared from **16**, under various conditions led to complex reaction mixtures. Of the chemical reducing agents employed the best result was

Table 1-1. ^{13}C NMR (50.3 MHz) data for the prepared compounds.

Compound	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	Ester C=O	S S	C-1'
5	$CDCl_3$	97.62	33.41	60.21	72.29	70.36	34.52	—	—	—
6	$CDCl_3$	98.88	35.25	59.29	79.37	153.79	96.77	—	—	—
7	$CDCl_3$	198.2	80.88	59.78	34.52	69.16	43.58	165.21	—	96.96
				60.20	36.27	69.97	45.90			97.43
8	Aceton d_6	69.56	80.70	60.46	33.76	69.07	43.24	165.56	39.37[a]	96.60
				60.82	36.19	69.56	46.40		41.69[a]	96.80
9	$CDCl_3$	67.50	75.86*	71.01*	35.85	66.34	47.18	165.08	39.13	—
								165.43	39.44	
10	Aceton d_6	68.75	80.00	60.38	36.92	65.58	47.85	166.08	39.28	—
									40.90	
11	Aceton d_6	69.20	88.29	61.60	37.05	65.34	47.61	—	39.38	—
									40.04	
12	$CDCl_3$	151.87	73.80	59.63	35.88*	64.92	31.14*	165.20	—	—
13	$CDCl_3$	67.59	71.15	71.15	—	76.34	—	165.23	—	104.62
								165.23		
								165.87		
								166.19		
14	$CDCl_3$	67.72	69.89	59.66	—	77.87	—	165.22	—	104.04
								165.30		
								165.64		
								166.15		
15	CD_3OD	71.42	70.87	62.49	—	82.75	—	—	—	107.30
16	$CDCl_3$	150.07	69.23	64.00	27.88*	74.84	35.40*	165.18	—	104.07
								165.22		
								165.35		
								166.04		
17	CD_3OD	157.06	71.10	64.28	28.58*	74.15	35.27*	—	—	107.54
18	CD_3OD	72.92	53.07	—	75.12	—	—	—	—	108.25
19	CD_3OD	72.25*	73.45*	—	75.08	—	—	—	—	107.87
22	Aceton d_6	67.36	79.59	60.26	32.65	70.49	46.10	165.20	39.72	107.21
									40.81	
23	Aceton d_6	64.12	82.13	61.89	32.90	70.00	44.72	—	39.14	106.28
									41.51	
24	Aceton d_6	68.74	80.73	55.53	31.95	70.04*	45.58	165.22	39.09	94.89
									41.42	
25	Aceton d_6	72.80	89.46	55.53	32.83	69.98*	45.11	—	39.16	95.48
									40.63	
26	Aceton d_6	69.36	80.60	60.28	36.06	67.18	46.11	164.70	39.34	95.36
								165.54	41.56	
27	Aceton d_6	68.90	80.50	60.60	36.13	69.10	43.41	164.55	39.11	96.00
								166.00	41.70	
29	Aceton d_6	68.86	80.40	60.57	36.78	71.19*	43.56	164.79	39.15	97.84
								165.80	41.66	
35	$CDCl_3$	97.23*	55.59	72.39	76.61	69.83	35.48	163.60	—	98.64*
38	DMSO d_6	200.46	77.47	80.02	54.15	69.92	45.00	165.12	—	99.67
								166.90		
								163.97		
								164.87		
								166.95		

* Signals are interchangeable.
[a] Double signal

obtained with lithium aluminium hydride, but the produced mixture of the diastereoisomeric diaminocyclitol-glycosides **20** and **21** still could not be separated. Hydrogenation of **28**, prepared from **26** upon Zemplén transesterification, over Raney nickel led to the unique aminocyclitol antibiotic model **31** built up from a dihydroxy-aminiocyclitol aglycone and a 3-amino-2,3,6-trideoxy-L-*arabino*-hexopyranose (L-acosamine)[15] sugar moiety.

An alternative, new strategy for preparing pseudo-disaccharide aminoglycoside antibiotics, structurally related to **31**, was based on the Ferrier carbocyclization of the reducing unit of disaccharides synthesized from amino(azido)deoxy sugar components. For such an approach methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[29,30] was converted, by means

Table 1-2. ^{13}C NMR (50.3 MHz) data for the prepared compounds.

Compound	Solvent	C-2′	C-3′	C-4′	C-5′	$-CH_2-$	OCH_2Ph	CH_3-5′	OCH_3	C-6′
5	$CDCl_3$	—	—	—	—	—	—	—	54.86	—
6	$CDCl_3$	—	—	—	—	—	73.73	—	55.10	—
7	$CDCl_3$	30.59	18.96	25.32	62.06	—	—	—	—	—
		30.74	19.59		63.02					
8	Aceton d_6	30.92	19.66	26.40	62.06	—	—	—	—	—
		31.60	19.80		62.31					
9	$CDCl_3$	—	—	—	—	—	—	—	—	—
10	Aceton d_6	—	—	—	—	—	—	—	—	—
11	Aceton d_6	—	—	—	—	—	76.36	—	—	—
12	$CDCl_3$	—	—	—	—	—	76.80	—	—	—
13	$CDCl_3$	←	77.92	→	63.81	35.14	—	—	—	—
			81.77			39.06				
			82.16			40.03				
						43.84				
14	$CDCl_3$	←	79.62	→	63.88	35.76	—	—	—	—
			81.63			38.64				
			82.03			40.76				
						43.11				
15	CD_3OD	←	82.75	→	63.03	36.94	—	—	—	—
			84.46			39.80				
			86.01			42.36				
						42.48				
16	$CDCl_3$	←	78.14	→	60.37	—	76.72	—	—	—
			81.99							
			82.75							
17	CD_3OD	←	78.81	→	62.88	—	76.85	—	—	—
			83.74							
			85.62							
18	CD_3OD	←	78.45	→	63.30	29.10	—	—	—	—
			84.07			29.30				
			85.24			37.90				
19	CD_3OD	←	78.75	→	63.07	28.37	—	—	—	—
			84.05			28.37				
			85.07			39.05				
22	Aceton d_6	←	82.65	→	67.10	—	—	—	—	—
			85.16							
			86.59							
23	Aceton d_6	←	86.53	→	71.42	—	—	—	—	—
			88.20							
			88.45							
24	Aceton d_6	70.89	71.75	73.01	59.98*	—	—	—	—	62.71
25	Aceton d_6	←	71.52	→	61.40*	—	76.47	—	—	62.69
			71.64							
			72.86							
26	Aceton d_6	33.66	58.70	77.90	70.60	—	—	17.88	—	—
27	Aceton d_6	35.73	58.79	76.21	71.10	—	—	18.46	—	—
29	Aceton d_6	36.08	60.57	77.60	71.62*	—	—	18.00	—	—
35	$CDCl_3$	31.30	57.00	76.61	66.54	—	—	17.08	53.50	—
38	DMSO d_6	35.88	58.69	76.28	66.36	—	—	17.36	—	—

* Signals are interchangeable.

of the Hanessian-Hullar method[31,32], into the 6-bromosugar **32**. This latter glycosyl acceptor was glycosylated with the 3-azido-1,4-di-*O*-(*p*-nitrobenzoyl)-2,3,6-trideoxy-α,β-L-*arabino* and *ribo*-hexopyranose donors[24] in the presence of trimethylsilyl triflate promoter, to obtain the α-disaccharides **34** and **35**, respectively. The formation of an α-glycosidic linkage was shown by the small values (3.5～4.0 Hz and 1.5～2.0 Hz) observed for the $J_{1',2'a}$ and $J_{1',2'e}$ coupling constants.

Dehydrobromination of **34** and **35**, to obtain the corresponding hex-5-enopyranosides failed under the conditions (AgF in pyridine, DBU in DMF or HMPA) successfully used[18] for various 6-bromo-6-deoxy-monosaccharides. Therefore, the 6-iodo analogue **36** of the disaccharide **35** was synthesized by glycosylation of the 6-iodo-glucosamine donor **33** (obtained from **32** by treatment with sodium iodide) with the L-*arabino*-3-azido-trideoxysugar donor. Reaction of the resulting 6-iodo-disaccharide **36** with silver(I)fluoride in pyridine readily furnished 85% of the desired unsaturated

Table 2-1. Characteristic ^{1}H NMR (200 MHz) data for the prepared compounds.

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6	OH	PhCH_2O
2	Aceton d_6	—	4.18	4.02	1.94 (a)	4.38	2.46 (a)	4.30	4.52
			(10.0)		2.25 (e)		2.78 (e)	(2.5)	4.92
5	$CDCl_3$	4.85	1.76 (a)	3.82	3.48	3.58~3.78		2.54	—
		(4.0, 1.0)	2.20 (e)		(9.5)	⟷			
6	$CDCl_3$	4.80	1.73 (a)	3.91	3.76	—	4.73	—	4.77
		(3.5, 1.75)	2.15 (e)				4.75		4.85
9	$CDCl_3$	—	5.57	5.57	2.14	4.30	2.52	2.14	—
10	Aceton d_6	—	5.32	4.22	1.89 (a)	4.20	2.45 (a)	4.12	—
					2.12 (e)		2.60 (e)		
11	Aceton d_6	—	3.59	4.15	1.68 (a)	4.03	2.25 (a)	3.88	4.88
			(7.5)	(9.0, 4.0)	1.96 (e)		2.40 (e)	(3.5)	
12	Aceton d_6	—	5.44	4.1~4.3	1.88 (a)	4.1~4.3	2.68 (a)	—	5.08
			(7.5)		2.21 (e)		2.97 (e)		
22	Aceton d_6	—	5.31	4.20	1.89 (a)	4.20	2.41 (a)	—	—
			(7.0)		1.96 (e)		2.63 (e)		
23	Aceton d_6	—	4.73	4.18	1.49 (a)	4.05	2.31 (a)	3.10	—
			(6.0)		2.18 (e)		2.43 (e)	3.12	
24	Aceton d_6	—	5.14	3.56	1.69 (a)	4.35	2.43 (a)	—	—
			(9.5)	(4.0, 12.5)	2.26 (e)		2.66 (e)		
25	Aceton e_6	—	3.44	3.56	1.48 (a)	4.08~4.40	2.28 (a)	—	4.78
			(9.0)		2.10 (e)		2.47 (e)		
26	Aceton d_6	—	5.37	4.22	1.98 (a)	4.22	2.58 (a)	—	—
			(9.0)		2.41 (e)		2.77 (e)		
27	Aceton d_6	—	5.36	4.11	1.98 (a)	4.35	2.55 (a)	—	—
			(9.5)		2.34 (e)		2.68 (e)		
28	Aceton d_6	—	4.74	3.68	1.68 (a)	4.00	2.40	3.06~3.32	—
					2.30 (e)			3.75~3.94	
29	Aceton d_6	—	5.35	4.18	1.96 (a)	4.34	1.78 (a)	—	—
			(9.5)		2.28 (e)		2.64 (e)		
32	$CDCl_3$	4.95	4.12	4.12	5.19	5.31	3.47	3.75	—
		(3.5)		(9.5)	(9.5)		3.57		
33	$CDCl_3$	4.93	4.48	4.08	5.11	3.94	3.25	1.72	—
		(4.0)		(9.5)	(9.5)		3.42		
34	$CDCl_3$	5.38	4.15	4.22	5.27	4.06	3.42~3.60	—	—
		(3.0)		(9.5)	(9.5)				
35	$CDCl_3$	4.85	4.76	4.22	5.36	4.14	3.39~3.57	—	—
		(3.5)		(9.5)	(9.5)				
36	$CDCl_3$	4.85	4.76	4.30	5.24	4.24	3.14~3.45	—	—
		(3.5)		(9.5)	(9.5)				
37	$CDCl_3$	4.88	4.60~4.90	4.33	4.60~4.90	—	5.39	—	—
		(2.5)					5.41		

Chemical shifts are given in ppm, coupling constants (in brackets) are given in Hz.
a = axial e = equatorial

compound **37**, as demonstrated by the appearance of the H-6 protons with chemical shifts δ 5.39 and 5.41 ppm, characteristic of those of the corresponding protons of related hex-5-enopyranosides[18].

Ferrier carbocyclization of the reducing unit of the unsaturated disaccharide **37** in the presence of mercuric chloride then gave the new 1→3 linked glycosylinosose 2*S*,3*R*,4*S*,5*S*-3-[3′-azido-4′-*O*-(*p*-nitrobenzoyl)-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyloxy]-2-*O*-benzoyl-4-benzamido-5-hydroxycyclohexanone **38** with 69% yield. Formation of the respective C-5 diastereoisomer was not observed, and the deoxyinosose structure of **38** was unequivocally proved by the ^{13}C NMR spectral data (Table 1), most particularly the appearance of the C-1 carbonyl signal at δ 200.4 ppm.

The present successful carbocyclization of **37** into **38** contributes to the scope of the Ferrier ring transformation reaction, proceeding under slightly acidic conditions[18,33], by claming that the reaction can be readily performed with such acid-labile disaccharides like the 2′-deoxy α-linked hex-5-enopyranoside **37**.

The prepared new pseudodisaccharides **18**~**21** and **31**, their azido(amino)-polydeoxycyclitol precursors, as well as the protected inosose-glycoside **38** are suitable candidates for obtaining another pseudotri- and tetrasaccharide aminocyclitol antibiotics by synthesis or chemical/biochemical modification.

Biological Properties

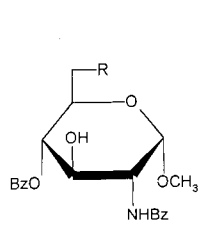
In *in vitro* tests on the most important Gram-positive

Table 2-2. Characteristic ^1H NMR (200 MHz) data for the prepared compounds.

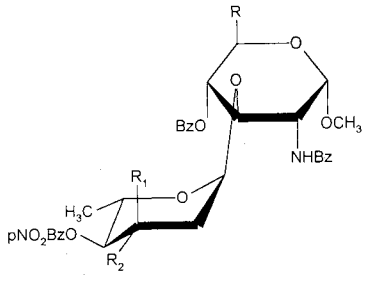
Compound	Solvent	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′	CH_3-5′	others
3	Aceton d_6	—	—	—	—	—	—	—	—
5	$CDCl_3$	—	—	—	—	—	—	—	OCH_3 3.38
6	$CDCl_3$	—	—	—	—	—	—	—	OCH_3 3.38
9	$CDCl_3$	—	—	—	—	—	—	—	—
10	Aceton d_6	—	—	—	—	—	—	—	—
11	Aceton d_6	—	—	—	—	—	—	—	—
12	Aceton d_6	—	—	—	—	—	—	—	—
22	Aceton d_6	5.31	4.95 (6.0)	4.79	4.55	4.55	—	—	CH_3 1.35 1.46
23	Aceton d_6	5.13	4.78 (6.0)	4.63	3.20	3.32	—	—	CH_3 1.31 1.42
24	Aceton d_6	4.32 (3.5)	5.77 (9.5)	5.79 (9.5)	5.18 (9.5)	4.18	4.12 4.20	—	CH_2CO 1.86 2.03 2.07
25	Aceton d_6	4.20 (2.5)	5.68 (9.5)	5.76 (9.5)	5.14 (9.5)	4.08～4.40 ⟷		—	CH_3CO 1.81 2.01 2.06
26	Aceton d_6	5.24 (3.5, 1.5)	1.98 (a) 2.41 (e)	4.30	4.95 (9.8, 9.8)	4.32	—	1.22 (6.0)	—
27	Aceton d_6	5.04 (3.5, 2.0)	1.98 (a) 2.26 (e)	4.59	5.04 (9.5)	4.19	—	1.29 (6.5)	—
28	Aceton d_6	4.99	1.47 (a) 2.10 (e)	3.75～3.94	4.61	3.75～3.95	—	1.23	—
29	Aceton d_6	4.98 (9.5, 2.5)	1.78 (a) 2.57 (e)	4.14	4.91 (9.5)	3.87	—	1.28 (6.0)	—
32	$CDCl_3$	—	—	—	—	—	—	—	OCH_3 3.55
33	$CDCl_3$	—	—	—	—	—	—	—	OCH_3 3.60
34	$CDCl_3$	4.87 (4.0, 2.0)	1.73～1.82	4.12	4.82 (3.5, 9.5)	4.06	—	1.30 (6.0)	OCH_3 3.45
35	$CDCl_3$	5.16 (3.5, 1.5)	1.55 (a) 2.09 (e)	3.85	4.64 (9.5)	3.74	—	1.21 (6.0)	OCH_3 3.54
36	$CDCl_3$	5.34 (3.5, 1.5)	1.62 (a) 1.97 (e)	3.94	4.66 (9.5)	3.81	—	1.28 (6.5)	OCH_3 3.50
37	$CDCl_3$	4.72 (3.0, 1.0)	1.70 2.06	3.85	4.60～4.90	3.30～3.60	—	1.28	OCH_3 3.50

Chemical shifts are given in ppm, coupling constants (in brackets) are given in Hz.
a = axial e = equatorial

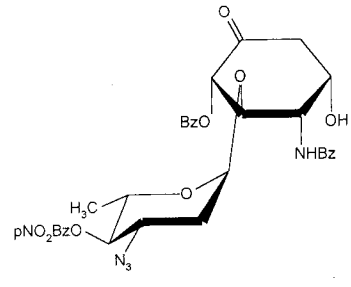
Fig. 4. The intermediates **32**～**36** and product **38** of the carbocyclization of the 2′-deoxy-disaccharide **37**.



32 R=Br
33 R=I



34 R=CH_2Br; R_1=N_3; R_2=H
35 R=CH_2Br; R_1=H; R_2=N_3
36 R=CH_2I; R_1=H; R_2=N_3
37 R=CH_2; R_1=H; R_2=N_3



38

and Gram-negative bacteria, using the agar dilution method, neither of the synthesized new deoxyinososes and pseudodisaccharide antibiotic models was found to show remarkable antibacterial activity (MIC > 100 μg/ml). In *Neurospora crassa* the azidoinososе **10** increased the amount of *myo*-inositol-1-phosphate synthase and inhibited the activity of *myo*-inositol-monophosphatase in 10 μg/ml concentration. The enhanced synthesis of *myo*-inositol-1-phosphate synthase was the cosequence of lowering the intracellular inositol concentration[34]. Li^+ treatment of *Neurospora crassa* has effects similar to those of the azidoinososе **10**.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 283 B instrument. ^1H (200 MHz) and ^{13}C NMR spectra (50.3 MHz) were recorded with a Bruker 200 SY spectrometer (internal TMS). Mass spectra were recorded with AEI-MS 902 and VG-7035 instruments. TLC and column chromatography were performed on Kieselgel 60 F_{254} (Merck) and Silica Gel 60 (Merck), using (*A*) 4:6 hexane-ether; (*B*) 9:1 toluene-ether; (*C*) 98:2 hexane-ether; (*D*) 98:2 chloroform-methanol; (*E*) 1:1 chloroform-hexane; (*F*) 9:1 toluene-ethyl acetate; (*G*) 96:4 toluene-ethyl acetate; (*H*) 8:2 toluene-methanol; (*I*) 8:2:0.8 methanol-toluene-25% aqueous NH_4OH; (*J*) 7:3 hexane-ethyl acetate; (*K*) 9:1 chloroform-acetone; (*L*) 5:5:0.1 dichloromethane-chloroform-ethyl acetate; (*M*) 98:2 toluene-methanol. Evaporations were carried out under diminished pressure at 35~40°C.

(2*S*,3*R*,5*R*)-3-Azido-2-benzyloxy-5-hydroxycyclohexanone (**3**)

To a solution of **6** (0.32 g, 1.16 mmol) in 2:1 acetone-water (15 ml) mercuric trifluoroacetate (0.05 g, 0.12 mmol) was added and the mixture was stirred for 3 hours. It was then concentrated, the residue was dissolved in dichloromethane (30 ml) and washed with 10% aq KI, 5% aq $NaHSO_3$ (10-10 ml) and water (2×5 ml). The organic layer was dried (Na_2SO_4), concentrated and the residue was subjected to flash column chromatography (*A*) to afford pure syrupy **3** (0.175 g, 57%), $[\alpha]_D$ +23.75° (*c* 0.8, $CHCl_3$).

Anal Calcd for $C_{13}H_{15}N_3O_3$: C 59.76, H 5.79, N 16.08.
Found: C 59.03, H 5.71, N 15.89.

Methyl 3-Azido-6-bromo-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (**5**)

A solution of **4** (3.85 g, 10.4 mmol)[18,19] in dry methanol (60 ml) was treated with 1 M sodium methoxide in methanol (1.5 ml) for 7 hours, neutralized with AG 50W×12 (H^+) ion exchange resin and evaporated. Column chromatography (*B*) of the residue gave pure syrupy **5** (2.72 g, 98%), $[\alpha]_D$ +120.2° (*c* 1.1, $CHCl_3$).

Anal Calcd for $C_7H_{12}N_3O_3Br$:
C 31.59, H 4.54, N 15.79, Br 30.03.
Found:
C 31.66, H 4.63, N 15.43, Br 30.46.

Methyl 3-Azido-4-*O*-benzyl-2,3,6-trideoxy-α-D-*threo*-hex-5-enopyranoside (**6**)

To a cold (0°C) solution of **5** (1.01 g, 3.8 mmol) in freshly distilled dry DMF (30 ml) 80% sodium hydride (0.684 g, 22.8 mmol) was portionwise added with vigorous stirring. After stirring at 0°C for 40 minutes. benzyl bromide (0.903 ml, 7.6 mmol) was dropwise added to the reaction mixture and the temperature was allowed to rise to 25°C. Stirring was continued for an additional 16 hours, the excess of sodium hydride was decomposed by the addition of dry methanol at 0°C and the mixture was concentrated. The residue was taken up with ethyl acetate (80 ml) and extracted with water (3×30 ml) and brine (2×10 ml). The combined aqueous layer was re-extracted with ethyl acetate (2×10 ml), the combined organic layer was dried (Na_2SO_4), concentrated and subjected to column chromatography (*C*) to yield pure syrupy **6** (0.92 g, 88%), $[\alpha]_D$ +64.4° (*c* 1.82, $CHCl_3$).

Anal Calcd for $C_{14}H_{17}N_3O_3$: C 61.08, H 6.22, N 15.26.
Found: C 60.59, H 6.24, N 14.83.

(2*S*,3*R*,5*R*)-3-Azido-2-benzoyloxy-5-(tetrahydropyranyloxy)-cyclohexanone (**7**)

A mixture of **2** (1 g, 0.28 mmol), 3,4-dihydro-2*H*-pyran (2 ml, 22 mmol) and *p*-toluenesulfonic acid (0.01 g) in dry benzene was stirred at room temperature for 90 minutes, when TLC (*D*) showed that all of the starting **2** had reacted. After neutralization by the addition of solid K_2CO_3 the mixture was diluted with dichloromethane (10 ml), washed with water (3×5 ml), dried (Na_2SO_4), concentrated and the residue was purified by column chromatography (*E*) to afford crystalline **7** (1.16 g, 89%), mp 94~97°C, $[\alpha]_D$ −72.7° (*c* 0.6, $CHCl_3$).

Anal Calcd for $C_{18}H_{21}N_3O_5$: C 60.15, H 5.89, N 11.69.
Found: C 59.89, H 6.00, N 11.87.

(2*S*,3*R*,5*R*)-3-Azido-2-benzoyloxy-5-(tetrahydropyranyloxy)-cyclohexanone Ethylene Dithioacetal (**8**)

A mixture of **10** (0.26 g, 0.74 mmol), 3,4-dihydro-2*H*-pyran (0.4 ml, 4.4 mmol) and *p*-toluenesulfonic acid (0.002 g) in dry benzene was stirred at room temperature for 2 hours. Working up of the reaction mixture as described above for the preparation of **7**, and purification by column chromatography (*F*) gave **8** (0.29 g, 90%), mp 99~102°C, $[\alpha]_D$ +15.9° (*c* 0.88, $CHCl_3$).

Anal Calcd for $C_{20}H_{25}N_3O_4S_2$:
C 55.14, H 5.78, N 9.65, S 14.72.
Found:
C 55.23, H 5.73, N 9.61, S 14.27.

Deprotection of the Carbonyl Function of **8** with Phenyl Dichlorophosphate[28]

To a mixture of **8** (0.11 g, 0.25 mmol), sodium iodide

(0.15 g, 1 mmol) and phenyl dichlorophosphate (0.064 g, 0.3 mmol) in dry acetonitrile (6 ml) one drop of dry DMF was added and the mixture was stirred at room temperature. After 15 hours TLC (*D*) showed that *ca.* 75% of **8** (Rf 0.9) had converted into **7** (Rf 0.75). The mixture was evaporated to dryness, the residue was taken up with dichloromethane and the organic solution was washed with water, dried (Na_2SO_4) and concentrated. Flash column chromatography (*E*) of the residue gave pure **7** (0.06 g, 66%), mp 95~97°C, $[\alpha]_D$ −72.4° (*c* 0.3, $CHCl_3$).

(2*S*,3*R*,5*R*)-2,3-Dibenzoyloxy-5-hydroxycyclohexanone Ethylene Dithioacetal (**9**)

To a solution of **1** (0.95 g, 2.68 mmol) and 1,2-ethanedithiol (5.0 ml, 59.4 mmol) in dry dichloromethane (95 ml) boron trifluoride etherate (1.0 ml) was added. After staying at room temperature for 1 hour TLC (*D*) showed the disappearance of **1**. The mixture was washed with 5% aq NaOH and water (3×10 ml), dried (Na_2SO_4), concentrated and co-evaporated with toluene. Trituration of the syrupy residue with dry ether resulted in the crystallization of **9**, which was filtered and washed with a cold 3:1 hexane-ether mixture (0.95 g, 82.5%), mp 131~132°C, $[\alpha]_D$ −43.3° (*c* 0.52, $CHCl_3$).

Anal Calcd for $C_{22}H_{22}O_5S_2$: C 61.37, H 5.16, S 14.89.
Found: C 61.18, H 5.09, S 14.61.

(2*S*,3*R*,5*R*)-3-Azido-2-benzoyloxy-5-hydroxycyclohexanone Ethylene Dithioacetal (**10**)

A mixture of **2** (1.10 g, 4 mmol) and 1,2-ethanedithiol (10 ml, 120 mmol) in dry dichloromethane (100 ml) was treated with boron trifluoride etherate (2.0 ml) as described for the preparation of **9**. After working up, the crude product was purified by means of column chromatography (*D*) to obtain pure **10** (1.21 g, 86%) as a foam, $[\alpha]_D$ +21.6° (*c* 1.41, $CHCl_3$).

MS *m/z* 351 (M, $C_{15}H_{17}N_3O_3S_2$), 323 (M−N_2), 305 (M−N_2−H_2O).

Anal Calcd for $C_{15}H_{17}N_3O_3S_2$: C 51.26, H 4.88, S 9.12.
Found: C 51.02, H 4.77, S 8.95.

(2*S*,3*R*,5*R*)-3-Azido-2-benzyloxy-5-hydroxycyclohexanone Ethylene Dithioacetal (**11**)

Compound **11** was prepared from **3** (1.38 g, 5.2 mmol) and 1,2-ethanedithiol (2.18 ml, 26 mmol) in dry dichloromethane (40 ml) in the presence of boron trifluoride etherate (1.5 ml) as described for the preparation of **9**. Column chromatography (*D*) gave pure syrupy **11** (1.23 g, 69%), $[\alpha]_D$ +19.2° (*c* 0.25, $CHCl_3$).

Anal Calcd for $C_{15}H_{19}N_3O_2S_2$:
C 53.38, H 5.67, N 12.45, S 19.00.
Found:
C 52.68, H 5.58, N 12.30, S 18.77.

(2*S*,3*R*,5*R*)-3-Azido-2-benzoyloxy-5-hydroxycyclohexanone *O*-Benzyl Oxime (**12**)

A solution of **2** (0.33 g, 1.2 mmol) in dry pyridine (8 ml) a solution of *O*-benzyl-hydroxylamine hydrochloride (0.21 g, 1.3 mmol) in dry methanol (5.0 ml) was added and the mixture was stirred at room temperature for 5 hours. It was then evaporated and co-evaporated with toluene to remove traces of pyridine. The residue was taken up with water, extracted with chloroform and the organic layer was sequentially washed with 10% aq $NaHCO_3$, water and then dried (Na_2SO_4). The syrupy residue, obtained upon evaporation of the solvent, crystallized and it was recrystallized from ether-hexane to give pure **12** (0.346 g, 76%), mp 89~90°C, $[\alpha]_D$ −58° (*c* 0.52, methanol), $[\alpha]_D$ −81° (*c* 1.05, $CHCl_3$).

MS *m/z* 380 (M, $C_{20}H_{20}N_4O_4$), 337 (M−HN_3).

Anal Calcd for $C_{20}H_{20}N_4O_4$: C 63.14, H 5.31, N 14.72.
Found: C 63.62, H 5.40, N 14.43.

(2*S*,3*R*,5*R*)-2,3-Dibenzoyloxy-5-(2′,3′,5′-tri-*O*-benzoyl-α-D-arabinofuranosyloxy)cyclohexanone Ethylene Dithioacetal (**13**)

A mixture of **9** (0.12 g, 0.28 mmol), mercuric bromide (0.10 g, 0.28 mmol) and freshly fused 4 Å molecular sieves (0.5 g) in dry dichloromethane (15 ml) was stirred in an argon atmosphere for 1 hour, and it was then treated with a cold dichloromethane solution of the glycosyl bromide prepared[21] from methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (0.31 g, 0.66 mmol) by treatment with 40% HBr in glacial acetic acid (3.50 ml). After stirring at room temperature for 16 hours the reaction mixture was diluted with dichloromethane, the insoluble materials were filtered off through a pad of Celite and the filtrate was sequentially washed with 10% aq $NaHCO_3$, 10% aq NaI, water and then dried (Na_2SO_4). Following evaporation, the crude product was purified by means of column chromatography (*G*) to afford pure **13** (0.204 g, 82%), mp 141~142°C, $[\alpha]_D$ −5.14° (*c* 0.74, $CHCl_3$).

Anal Calcd for $C_{48}H_{42}O_{12}S_2$: C 65.88, H 4.84, S 7.33.
Found: C 64.43, H 4.69, S 7.41.

(2*S*,3*R*,5*R*)-3-Azido-2-benzoyloxy-5-(2′,3′,5′-tri-*O*-benzoyl-α-D-arabinofuranosyloxy)-cyclohexanone Ethylene Dithioacetal (**14**)

A mixture of **10** (0.203 g, 0.58 mmol), mercuric bromide (0.208 g, 0.58 mmol) and freshly fused 4 Å molecular sieves (0.5 g) in dry dichloromethane (15 ml) was stirred at room temperature for 2 hours and then treated with a dichloromethane solution of the glycosyl bromide prepared from methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (0.413 g, 0.87 mmol) with 40% HBr in glacial acetic acid (4.0 ml). After stirring at room temperature for 18 hours the mixture was worked up as described above for the preparation of **13**. The crude product obtained upon evaporation was purified by means of column chromatography (*G*) to isolate pure syrupy **14** (0.346 g, 75.3%), $[\alpha]_D$ +3.4° (*c* 1.06, $CHCl_3$).

MS *m/z* 648 (M−$C_7H_5O_3$−N_3), 446 ($C_{26}H_{22}O_7$), 305 ($C_{15}H_{15}NO_2S_2$).

Anal Calcd for $C_{41}H_{37}N_3O_{10}S_2$:
C 61.87, H 4.68, N 5.28, S 8.06.

Found:
C 61.48, H 4.59, N 5.12, S 8.22.

(2*S*,3*R*,5*R*)-3-Azido-2-benzoyloxy-5-(2′,3′,5′-tri-*O*-benzoyl-α-D-arabinofuranosyloxy)-cyclo-hexanone *O*-Benzyl Oxime (**16**)

A mixture of **12** (0.11 g, 0.29 mmol), mercuric bromide (0.1 g, 0.29 mmol), and freshly fused 4 Å molecular sieves (0.5 g) in dry dichloromethane (10 ml) was stirred at room temperature for 2 hours and then treated with a dichloromethane solution of the glycosyl bromide prepared from methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (0.206 g, 0.43 mmol) with 40% HBr in glacial acetic acid (2.0 ml). After stirring at room temperature for 24 hours the reaction mixture was worked up as described above for the preparation of **13**. Purification of the crude product by means of column chromatography (*G*) afforded pure **16** as a syrup (0.185 g, 78%), $[\alpha]_D$ −55.5° (*c* 1.2, $CHCl_3$).

Anal Calcd for $C_{46}H_{40}N_4O_{11}$: C 66.98, H 4.89, N 6.79.
Found: C 66.63, H 4.81, N 6.46.

(2*S*,3*R*,5*R*)-3-Azido-2-hydroxy-5-(α-D-arabinofuranosyloxy)-cyclohexanone *O*-Benzyl Oxime (**17**)

A solution of **16** (0.240 g, 0.3 mmol) in dry methanol (5.0 ml) was treated with 0.1 M sodium methoxide in methanol (0.8 ml) at room temperature for 16 hours and then neutralized with AG 50W × 12 (H^+) ion exchange resin. The resin was filtered off, the filtrate was concentrated and the residue was subjected to column chromatography (*H*) to furnish pure syrupy **17** (0.12 g, 97%), $[\alpha]_D$ +16.8° (*c* 1.0, methanol).

Anal Calcd for $C_{18}H_{24}N_4O_7$: C 52.93, H 5.92, N 13.72.
Found: C 53.24, H 5.88, N 13.51.

(1*R*,2*R*,4*S*)-2-Amino-1-hydroxy-4-(α-D-arabinofuranosyloxy)-cyclohexane (**18**)

A solution of **14** (0.32 g, 0.4 mmol) in dry methanol (20 ml) was treated with a catalytic amount of sodium methoxide (0.1 M in methanol) for 8 hours and then neutralized with AG 50W × 12 (H^+) cation exchange resin. Following filtration of the resin the filtrate was concentrated and the residue was purified by means of column chromatography (*H*) to give **15** (0.13 g, 86%), $[\alpha]_D$ +95° (*c* 1.1, methanol).

A mixture of **15** (0.12 g, 0.32 mmol) and freshly prepared Raney nickel (0.05 g) in dry methanol was hydrogenated at atmospheric pressure for 18 hours. The catalyst was filtered off through a pad of Celite, the filtrate was concentrated and the residue was subjected to column chromatography (*I*) to isolate pure syrupy **18** (0.044 g, 52%), $[\alpha]_D$ +106.8° (*c* 2.0, methanol).

Anal Calcd for $C_{11}H_{21}NO_6$: C 50.16, H 8.04, N 5.32.
Found: C 51.38, H 7.97, N 5.22.

(1*R*,2*R*,4*S*)-1,2-Dihydroxy-4-(α-D-arabinofuranosyloxy)-cyclohexane (**19**)

A solution of **13** (0.27 g, 0.3 mmol) in dry methanol (10 ml) was treated with 1 M sodium methoxide in methanol (0.05 ml) for 24 hours. Following neutralization with AG 50W × 12 (H^+) ion exchange resin freshly prepared Raney nickel (0.25 g) was added and the mixture was vigorously stirred for 7 hours. After filtration and evaporation, the syrupy residue was subjected to column chromatography (*H*) to furnish pure **19** (0.032 g, 39%), $[\alpha]_D$ +84.5° (*c* 0.78, methanol).

Anal Calcd for $C_{11}H_{20}O_7$: C 49.99, H 7.63.
Found: C 48.76, H 7.58.

Reduction of the Pseudodisaccharide **17** with Lithium Aluminium Hydride

A mixture of **17** (0.1 g, 0.25 mmol) and lithium aluminium hydride (0.15 g) in dry ether (10 ml) was stirred at room temperature for 3 hours. Following decomposition of the excess of the reagent by dropwise addition of ethyl acetate and water the organic layer was separated, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry ether (10 ml), trifluoroacetic anhydride (0.5 ml) was added and the reaction mixture was kept at room temperature for 3 hours. It was then cooled to 0°C, dry methanol (3.0 ml) was added dropwise while cooling, and the mixture was concentrated and co-evaporated three times with toluene. TLC examination of the syrupy residue (*D*) showed the presence of two major products (Rf 0.73 and 0.78) in a *ca.* 1 : 1 ratio. Purification of this mixture by means of column chromatography (gradient elution: chloroform→98 : 2 chloroform - methanol) gave a syrupy mixture of **20** and **21** which could not be further separated (0.092 g, 80%).

Anal Calcd for $C_{15}H_{20}N_2O_8F_6$: C 38.30, H 4.29, N 5.96.
Found: C 37.89, H 4.11, N 5.68.

(2*S*,3*R*,5*R*)-3-Azido-2-benzoyloxy-5-(2′,3′-*O*-isopropylidene-5′-*O*-*p*-nitrobenzoyl-α-D-ribofuranosyloxy)-cyclohexanone Ethylene Dithioacetal (**22**) and Its *O*-Deacylated Derivative **23**

A mixture of **10** (0.214 g, 0.61 mmol), 2,3-*O*-isopropylidene-1,5-di-*O*-*p*-nitrobenzoyl-α,β-D-ribofuranose (0.3 g, 0.61 mmol)[22] and 4 Å molecular sieves (0.08 g) in dry dichloromethane (8 ml) was stirred in a nitrogen atmosphere for 30 minutes, cooled to −70°C and trimethylsilyl triflate (150 ml, 0.71 mmol) was added. The temperature was allowed to rise to 25°C and stirring was continued for additional 7 hours. The mixture was diluted with dichloromethane (16 ml) and poured to 5% aq $NaHCO_3$ (10 ml). After separation, the organic layer was washed with 5% aq $NaHCO_3$ (10 ml) and water (2 × 10 ml), dried (Na_2SO_4), concentrated and the residue was subjected to column chromatography (*J*) to obtain **22** (0.18 g, 42.5%) as a syrup, $[\alpha]_D$ −15° (*c* 0.64, $CHCl_3$).

Anal Calcd for $C_{30}H_{32}N_4O_{10}S_2$:
C 53.56, H 4.79, N 8.32, S 9.51.
Found:
C 53.69, H 4.71, N 8.03, S 9.87.

Zemplén *O*-deacylation of **22** (0.15 g, 0.22 mmol) with 1 M sodium methoxide in methanol and subsequent column chromatography furnished syrupy **23** (0.065 g,

69%), $[\alpha]_D$ −28.1° (*c* 1.21, $CHCl_3$).

(2*S*,3*S*,5*R*)-3-Azido-2-benzoyloxy-5-(2′-deoxy-2′-phthalimido-3′,4′,6′-tri-*O*-acetyl-α-D-glucopranosyloxy)-cyclohexanone Ethylene Dithioacetal (**24**)

Glycosylation of **10** (0.135 g, 0.38 mmol) with 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-α,β-D-glucopyranose (0,148 g, 0.38 mmol)[23] in dry dichloromethane and in the presence of 4 Å molecular sieves (70 mg) and trimethylsilyl triflate promoter (180 μl, 0.92 mmol) was performed as described for the preparation of **22**. The crude product was purified by means of column chromatography (*L*) to give pure syrupy **24** (0.082 g, 28%), $[\alpha]_D$ −11.8° (*c* 1.09, $CHCl_3$).

Anal Calcd for $C_{35}H_{36}N_4O_{12}S_2$:
C 54.67, H 4.68, N 7.32, S 8.32.
Found:
C 53.88, H 4.69, N 7.21, S 8.00.

(2*S*,3*R*,5*R*)-3-Azido-2-benzyloxy-5-(2′-deoxy-2′-phthalalimido-3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranosyloxy)-cyclohexanone Ethylene Dithioacetal (**25**)

Glycosylation of **11** (0.183 g, 0.54 mmol) with 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-α,β-D-glucopyranose (0.286 g, 0.6 mmol) in dry dichloromethane (10 ml) and in the presence of 4 Å molecular sieves (80 mg) and trimethylsilyl triflate promoter (130 μl, 0.66 mmol) was performed as described above for the preparation of **22**. Column chromatography (*M*) resulted in pure **25** (0.13 g, 31%).

Anal Calcd for $C_{35}H_{38}N_4O_{11}S_2$:
C 55.69, H 5.07, N 7.42, S 8.49.
Found:
C 55.41, H 4.96, N 7.22, S 8.13.

(2*S*,3*R*,5*R*)-3-Azido-2-benzoyloxy-5-[3′-azido-4′-*O*-*p*-nitrobenzoyl-2′,3′,6′-trideoxy-α-(**26**) and β-(**29**) L-*arabino*-Hexopyranosyloxy]-cyclohexanone Ethylene Dithioacetal

A mixture of 3-azido-1,4-di-*O*-(*p*-nitrobenzoyl)-2,3,6-trideoxy-α,β-L-*arabino*-hexopyranose (0.3 g, 0.64 mmol)[24] and freshly fused 4 Å molecular sieves (0.08 g) in dry dichloromethane (3 ml) was stirred in an argon atmosphere for 2 hours. It was then cooled to −70°C and trimethylsilyl triflate (120 μl, 0.64 mmol) was added. The temperature was allowed to rise to −20°C and a cold (−20°C) solution of **10** (0.30 g, 0.85 mmol) in dry dichloromethane (3.0 ml) was added. The reaction mixture was kept at −20°C for 3 days, when TLC (*J*) showed the formation of two new products (Rf 0.37 and 0.23). Following dilution with dichloromethane (10 ml) the mixture was washed with 5% aq $NaHCO_3$ and water (3 × 10 ml), dried (Na_2SO_4) and evaporated. The residue was subjected to column chromatography (*J*) to isolate, first the a anomer **26** (0.28 g, 67%), Rf 0.37, $[\alpha]_D$ +19.1° (*c* 0.69, $CHCl_3$).

Anal Calcd for $C_{28}H_{29}N_7O_8S_2$:
C 51.28, H 4.46, N 14.95, S 9.78.
Found:
C 51.11, H 4.53, N 14.95, S 9.48.

Eluted second was the β anomer **29** (0.03 g, 7%), Rf 0.23, $[\alpha]_D$ +47.4° (*c* 0.73, $CHCl_3$).

(2*S*,3*R*,5*R*)-3Azido-2-benzoyloxy-5-(3′-azido-4′-*O*-*p*-nitrobenzoyl-2′,3′,6′-trideoxy-α-L-*ribo*-hexopyranosyl-oxy)-cyclohexanone Ethylene Dithioacetal (**27**)

Glycosylation of **10** (0.2 g, 0.57 mmol) with 3-azido-1,4-di-*O*-(*p*-nitrobenzoyl)-2,3,6-trideoxy-α,β-L-*ribo*-hexopyranose (0.28 g, 0.6 mmol)[24] in dry dichloromethane (3 ml) and in the presence of 4 Å molecular sieves (0.08 g) and trimethylsilyl triflate promoter (0.1 ml) was performed as described above for the preparation of **26**. Purification of the crude product by means of column chromatography (*G*) yielded pure **27** (0.23 g, 61%), Rf 0.28, $[\alpha]_D$ +92.3° (*c* 0.66, $CHCl_3$).

Anal Calcd for $C_{28}H_{29}N_7O_8S_2$:
C 51.28, H 4.46, N 14.95, S 9.78.
Found:
C 51.90, H 4.51, N 14.77, S 9.61.

(1*R*,2*R*,4*S*)-2-Amino-1-hydroxy-4-(3′-amino-2′,3′,6′-trideoxy-α-L-*arabino*-hexopyranosyloxy)-cyclohexane (**31**)

A solution of **26** (0.22 g, 0.34 mmol) in dry methanol (10 ml) was treated with 3 drops of 1 M sodium methoxide in methanol for 16 hours. It was then neutralized with AG 50W × 12 (H^+) ion exchange resin, the resin was filtered off and the filtrate was evaporated to dryness. The syrupy residue was subjected to column chromatography (*H*) to obtain 0.117 g (87%) of syrupy **28**, $[\alpha]_D$ +82.6° (*c* 0.8, methanol).

A mixture of **28** (0.1 g, 0.25 mmol) and freshly prepared Raney nickel (0.025 g) in dry methanol (10 ml) was hydrogenated for 20 hours. TLC examination (*I*) showed the formation of a new product (Rf 0.78). The catalyst was filtered off, the filtrate was evaporated and the residue was subjected to column chromatography (*H*) to afford pure syrupy **31** (0.041 g, 62.5%), $[\alpha]_D$ +88.7° (*c* 0.7, methanol).

Anal Calcd for $C_{12}H_{24}N_2O_4$: C 55.36, H 9.29, N 10.76.
Found: C 54.88, H 9.20, N 11.03.

Methyl 2-Benzamido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-glucopyranoside (**32**)

A mixture of methyl 2-benzamido-4,6-*O*-benzylidene-α-D-glucopyranoside (0.77 g 2 mmol)[29,30], *N*-bromosuccinimide (0.44 g, 2.46 mmol) and freshly dried $BaCO_3$ (0.3 g, 3 mmol) in dry carbon tetrachloride (20 ml) was stirred under reflux for 3 hours. After filtration while hot, the filtrate was washed with 10% aq $NaHSO_3$ (3 × 2 ml), water (3 × 3 ml), dried (Na_2SO_4) and concentrated. Recrystallization of the crude product from methanol gave **32** (0.58 g, 63.5%), mp 182~183°C.

Anal Calcd for $C_{21}H_{22}NO_6Br$: C 54.41, H 4.78, Br 17.25.
Found: C 53.78, H 4.66, Br 17.19.

Methyl 2-Benzamido-4-*O*-benzoyl-2,6-dideoxy-6-iodo-α-D-glucopyranoside (**33**)

A mixture of **32** (0.93 g, 2 mmol) and dry sodium iodide (0.72 g, 4.8 mmol) in dry butanone (60 ml) was refluxed for 4 hours and filtered while hot. The residue obtained upon evaporation was extracted with chloroform (3 × 20 ml) and the organic solution was washed with 5% aq $NaHSO_3$ (3 × 3 ml), 10% aq $NaHCO_3$ and water and then dried (Na_2SO_4). Following evaporation the crystalline residue was recrystallized from methanol-hexane to obtain **33** (0.76 g, 75%), mp 168~171°C (dec.).

Anal Calcd for $C_{21}H_{22}NO_6I$: C 49.33, H 4.34, I 24.82.
Found: C 48.89, H 4.29, I 24.97.

Methyl 3-*O*-(3'-Azido-4'-*O*-*p*-nitrobenzoyl-2',3',6'-trideoxy-α-L-*ribo*-hexopyranosyl)-2-benzamido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-glucopyranoside (**34**)

Glycosylation of **32** (0.075 g, 0.17 mmol) with 3-azido-1,4-di-*O*-(*p*-nitrobenzoyl)-2,3,6-trideoxy-α,β-L-*ribo*-hexopyranose (0.08 g, 0.17 mmol)[24] in dry dichloromethane (10 ml) and in the presence of 4 Å molecular sieves (0.15 g) and trimethylsilyl triflate promoter (20 ml) was performed as described for the preparation of **26**. Column chromatography (*J*) gave pure **34** (0.053 g, 41%), mp 116~118°C, $[\alpha]_D$ −42.8° (*c* 0.5, $CHCl_3$).

Anal Calcd for $C_{34}H_{34}N_5O_{11}Br$: N 9.11, Br 10.40.
Found: N 9.05, Br 10.31.

Methyl 3-*O*-(3'-Azido-4'-*O*-*p*-nitrobenzoyl-2',3',6'-trideoxy-α-L-*arabino*-hexopyranosyl)-2-benzamido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-glucopyranoside (**35**)

The reaction of **32** (0.5 g, 1.08 mmol) with 3-azido-1,4-di-*O*-(*p*-nitrobenzoyl)-2,3,6-trideoxy-α,β-L-*arabino*-hexopyranose (0.51 g, 1.08 mmol)[24] in dry dichloromethane (70 ml) and in the presence of 4 Å molecular sieves (0.7 g) and trimethylsilyl triflate promoter (0.1 ml) was carried out as described for the preparation of **26**. Column chromatography (*J*) gave pure **35** (0.3 g, 36%), mp 198~200°C, $[\alpha]_D$ −33.4° (*c* 0.5, $CHCl_3$).

Anal Calcd for $C_{34}H_{34}N_5O_{11}Br$: N 9.11, Br 10.40.
Found: N 9.03, Br 10.28.

Methyl 3-*O*-(3'-Azido-4'-*O*-*p*-nitrobenzoyl-2',3',6'-trideoxy-α-L-*arabino*-hexopyranosyl)-2-benzamido-4-*O*-benzoyl-2,6-dideoxy-6-iodo-α-D-glucopyranoside (**36**)

Glycosylation of **33** (0.6 g, 1.17 mmol) with 3-azido-1,4-di-*O*-(*p*-nitrobenzoyl)-2,3,6-trideoxy-α,β-L-*arabino*-hexopyranose (0.55 g, 1.17 mmol) in dry dichloromethane (65 ml) and in the presence of 4 Å molecular sieves (0.7 g) and trimethylsilyl triflate promoter (0.1 ml) was performed as described for the preparation of **26**. Column chromatography furnished **36** (0.347 g, 42%), mp 182~184°C, $[\alpha]_D$ −30° (*c* 0.5, $CHCl_3$).

Anal Calcd for $C_{34}H_{34}N_5O_{11}I$: N 8.59, I 15.56.
Found: N 8.50, I 15.60.

Methyl 3-*O*-(3'-Azido-4'-*O*-*p*-nitrobenzoyl-2',3',6'-trideoxy-α-L-*arabino*-hexopyranosyl)-2-benzamido-4-*O*-benzoyl-2,6-dideoxy-α-D-*xylo*-hex-5-enopyranoside (**37**)

A mixture of **36** (0.238 g, 0.29 mmol) and carefully dried silver (I) fluoride (0.14 g) in dry pyridine (1.5 ml) was stirred in the dark for 24 hours. It was then poured into dry ether (50 ml), the organic solution was decanted from the dark residue, filtered through a thin pad of Celite, concentrated and co-evaporated with toluene. A solution of the residue in ether was passed through a small Silica gel column. Evaporation of the eluate gave pure **37** (0.171 g, 85%), mp 132~134°C, $[\alpha]_D$ −48.3° (*c* 0.5, $CHCl_3$).

Anal Calcd for $C_{34}H_{33}N_5O_{11}I$:
C 59.38, H 4.84, N 10.19.
Found:
C 58.83, H 4.80, N 10.00.

(2*S*,3*S*,4*S*,5*S*)-3-(3'-Azido-4'-*O*-*p*-nitrobenzoyl-2',3',6'-trideoxy-α-L-*arabino*-hexopyranosyloxy)-4-benzamido-2-*O*-benzoyl-5-hydroxycyclohexanone (**38**)

Compound **37** (0.171 g, 0.25 mmol) and mercuric chloride (0.068 g, 0.25 mmol) were dissolved in a mixture of acetone (1.9 ml) and water (0.9 ml) and refluxed for 3.5 hours, when TLC (*K*) showed that all of **37** had reacted. The solid precipitate was filtered off, washed with aqueous acetone, the combined filtrate was evaporated to dryness, the residue was taken up with chloroform (50 ml), and this solution was washed with water (3 × 6 ml). After drying (Na_2SO_4) and evaporation crystalline **38** was isolated (0.116 g, 69%), mp 233~234°C, $[\alpha]_D$ +42° (*c* 0.35, pyridine).

Anal Calcd for $C_{33}H_{31}N_5O_{11}$: C 58.83, H 4.64, N 10.40.
Found: C 59.32, H 4.58, N 10.29.

Acknowledgments

The authors thank Dr. S. ŌMURA (Kitasato Institute, Tokyo) and Dr. G. SZABÓ (University Medical School, Debrecen) for the biological investigations. Financial support for this work was obtained from the Grants OTKA 7418 and OTKA 1181 given by the National Science Foundation (Hungary).

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