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SYNTHESES OF HOMOLOGOUS ω-AMINATED 1-METHOXYALKYL β-D-GLUCOPYRANOSIDES AS POTENTIAL β-D-GLUCOSIDASE INHIBITORS*

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ABSTRACT

(*R*)- and (*S*)-2-Azido-1-methoxyethyl β-D-glucopyranosides (**16**) and (**17**), (*R*)- and (*S*)-3-azido-1-methoxypropyl β-D-glucopyranosides (**18**) and (**19**), (*R*,*S*)-4-azido-1-methoxybutyl β-D-glucopyranoside (**20**), and (*R*,*S*)-5-azido-1-methoxypentyl β-D-glucopyranoside (**22**) were synthesized from ω-substituted dimethyl acetals of acetaldehyde, propanal, butanal, and pentanal by trimethylsilyl triflate-catalysed transacetalation using 1-*O*-trimethylsilyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucose (**1**) as acceptor. Most of the acetylated (*R*,*S*)-epimers could be resolved into pure compounds by column chromatography. Preliminary tests showed that the deacetylated acetal glucosides carrying ω-bromo, azido, or acetamido substituents in the aglycon are good substrates for β-D-glucosidase from sweet almonds. The corresponding ω-amino derivatives of compounds **16, 19, 20,** and **22**, (*R*)-2-amino-1-methoxyethyl β-D-glucopyranoside (**23**), (*S*)-3-amino-1-methoxypropyl β-D-glucopyranoside (**24**), (*R*,*S*)-4-amino-1-methoxybutyl β-D-glucopyranoside (**25**), and (*R*,*S*)-5-amino-1-methoxypentyl β-D-glucopyranoside (**26**) proved almost completely resistant to β-D-glucosidase. The stability of the glucosides against enzyme hydrolysis is dependent on the distance between the amino group and the anomeric center.

INTRODUCTION

Aminated 1-methoxyalkyl α-D-glucopyranosides, although quite sensitive to aqueous acid[2], have been shown[1] to be hydrolysis-resistant, competitive inhibitors of α-D-glucosidase from yeast. These findings are in agreement with results of extensive investigations on carbohydrate derivatives containing amino groups[3–6]. According to Legler *et al.*[3] and depending on the glycosidase, either a free amino group or an ammonium group in a substrate analogue is responsible for the inhibitory power. 1-Alkoxyalkyl glycosides carrying an amino function in the aglycon are, to our knowledge, the only synthetic glycosides yet tested that are capable of

*Dedicated to Dr. R. Stuart Tipson.

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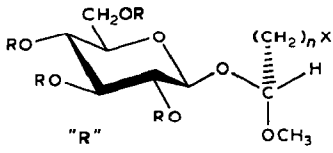
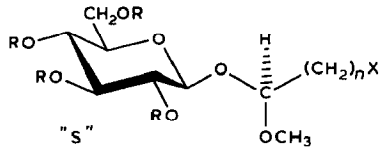
preventing (by the presence of this function) their own otherwise facile, enzymic acid hydrolysis[2]. Acylation of the amino group turns these glycosides back into ordinary, cleavable substrates for α-D-glucosidase[7]. It is reasonable to assume that shifting an amino group further away from the glycosidic bond might decrease its capability to function as a counter ion for a catalytically essential, proton-donating group from the enzyme. In this paper we describe syntheses of four diastereomeric pairs of ω-aminated 1-methoxyalkyl β-D-glucopyranosides differing in the length of the aglyconic alkyl chain. β-D-Glucosides were investigated instead of α-D-glucosides in order also to resolve the question as to whether the inhibitory properties of aminated 1-alkoxyalkyl glycosides against the corresponding glycosidases are restricted to α-D-glucosidase from yeast or whether this could be a general phenomenon.





	R	n	X		R	n	X
6	Ac	1	Br	**7**	Ac	1	Br
8	Ac	1	N_3	**9**	Ac	1	N_3
10	Ac	2	N_3	**11**	Ac	2	N_3
12	Ac	3	Br	**13**	Ac	3	Br
14	Ac	3	N_3	**15**	Ac	3	N_3
16	H	1	N_3	**17**	H	1	N_3
18	H	2	N_3	**19**	H	2	N_3
20[a]	H	3	N_3	**24**	H	2	NH_2
21[a]	H	3	NHOAc				
22[a]	H	4	N_3				
23	H	1	NH_2				
25[a]	H	1	NH_2				
26[a]	H	4	NH_2				
37[a]	Ac	3	NHOAc				
38[a]	Ac	4	N_3				

[a] Diastereomeric mixture

RESULTS AND DISCUSSION

The most convenient method for the preparation of 1-methoxyalkyl β-glycosides has been published by Tietze[8]. 2,3,4,6-Tetra-*O*-acetyl-1-*O*-trimethylsilyl-β-D-glucose (**1**) may be acetalated at the anomeric carbon atom with retention of configuration by using suitable ω-substituted (either bromo or azido) alkanal dimethyl acetals. 2-Bromoacetaldehyde dimethyl acetal (**2**) is the only commercially available starting material. The corresponding derivatives (**3**–**5**) of propanal, butanal, and pentanal had to be prepared by conventional methods.

$(MeO)_2HC(CH_2)_nCH_2R$

2 $n = 0$, R = Br
3 $n = 1$, R = N_3
4 $n = 2$, R = Br
5 $n = 3$, R = N_3

The structures of these actals were confirmed by ^{1}H-n.m.r. and i.r. spectroscopy and by the preparation of 2,4-dinitrophenylhydrazones. For compounds **2** and **4**, the ω-azido group was introduced after the glycosides had been prepared. Acetalation of **1** by compounds **2–5** gave rise in each instance to a pair of diastereomers.

Separation by t.l.c. was possible (Table I) for the homologues derived from **2, 3,** and **4**, namely (*R*)-2-bromo-1-methoxyethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**6**) and (*S*)-2-bromo-1-methoxyethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**7**), (*R*)-2-azido-1-methoxyethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**8**) and (*S*)-2-azido-1-methoxyethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**9**), (*R*)-3-azido-1-methoxypropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**10**) and (*S*)-3-azido-1-methoxypropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**11**), (*R*)-4-bromo-1-methoxybutyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**12**) and (*S*)-4-bromo-1-methoxybutyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**13**), and (*R*)-4-azido-1-methoxybutyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**14**) and (*S*)-4-azido-1-methoxybutyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**15**). On a preparative scale, only the pairs **6/7** and **10/11** were separable by flash chromatography[9] into pure components. The slower-migrating diastereomers were formed in higher yields and certain ^{1}H-n.m.r. signals as well as optical rotations in one series of homologues differ from those of their diastereomers in a parallel fashion (Table II).

The absolute configuration at the newly formed asymmetric acetal carbon atom C-1′ in compound **6** and its diastereomer **7** may be readily determined by ^{1}H-n.m.r. analysis of the *trans*-decalin system formed after intramolecular substitution of bromine in the deacetylated compounds. A configurational assignment of the corresponding α-D-glucopyranosides had already been carried out[1]. From the coupling constants between the proton at C-1′ and the two protons at C-2′ (Table III) the faster-migrating 2-bromo-1-methoxyethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**6**) was shown to have the *R*-configuration at C-1′ and the slower-migrating diastereomer **7** the *S*-configuration.

It is reasonable to assume that the homologues in one series differ from their diastereomeric counterparts of the other series by the same physical characteristics (certain ^{1}H-n.m.r. signals, $[\alpha]_D$, and chromatographic mobility). As the faster-migrating component **6** of the diastereomeric pair **6/7** has the *R*-configuration at the newly formed acetal carbon atom, we propose that all of the faster-migrating diastereomers of a given pair are related likewise. As shown in Table I, the characteristic ^{1}H-n.m.r. signals of the methoxy group, the anomeric hydrogen atom, and the hydrogen atom at C-1′ in all compounds in the same series are subject to the

TABLE I

DIAGNOSTIC DATA FOR DIASTEREOMERIC PAIRS OF ACETAL GLUCOSIDES

Diastereomeric pairs of acetylated acetal glucosides		R_F *Values*[a]		*^{1}H-N.m.r. signals (p.p.m.)*						$[\alpha]_D^{23}$ (*c*, 1.0)	
Slower migr.	*Faster migr.*	*Slow*	*Fast*	*H-1*		*H-1'*		*OCH_3*		*Slow*	*Fast*
				Slow	*Fast*	*Slow*	*Fast*	*Slow*	*Fast*		
7	**6**	0.30	0.32			4.90	4.78	3.41	3.45	−40.0	−25.5
9	**8**	0.25	0.29			4.83	4.69	3.44	3.46	−41.0	−25.0
11	**10**	0.27	0.30			4.85	4.70	3.35	3.41	−32.0	−19.5
13	**12**	0.34	0.35			4.79	4.60	3.32	3.39		
15	**14**	0.27	0.28			4.78	4.59	3.32	3.39	−36.0	−33.5
Diastereomeric pairs of deacetylated compounds										$[\alpha]_D^{23}$[b]	
17	**16**			4.71	4.63	5.03	4.90	3.52	3.54	−30.5	−38.0
19	**18**			4.69	4.59	5.02	4.88	3.46	3.50	−39.0	−44.5

[a]Silica gel 60, solvent *A*. [b]Because of the different solvent used, the order of higher to lower optical rotation is reversed in deacetylated compounds.

TABLE II

^{1}H-N.M.R. DATA [a] (250 MHz)

Proton	*Compound*							
	4	**5**	**27**	**28**	**29**	**31**	**32**	**33**
H-1a	4.40 t	4.36 t	4.10 dd	4.02 dd	4.08 dd	4.01–4.15 m	3.97–4.07 m	4.04 t
H-1b			3.60 dd	3.52 dd	3.57 dd	3.52 t	3.46 t	3.52 t
H-2	1.71–1.98 m	1.56–1.70 m	4.28 p	4.06–4.22 m	4.18 p	4.01–4.15 m	3.97–4.07 m	4.09 p
H-3	1.71–1.98 m	1.45 m	1.83 q	1.90 dt	1.77–1.87 m	1.43–1.73 m	1.30–1.76 m	1.45–1.71 m
H-4	3.44 t	1.56–1.70 m	3.79 q	4.06–4.22 m	3.44 dt	1.43–1.73 m	1.30–1.76 m	1.45–1.71 m
H-5		3.28 t				1.43–1.73 m	1.30–1.76 m	1.45–1.71 m
H-6						3.64 t	3.97–4.07 m	3.30 t
H-O			2.59 t			1.97 t		
Bn				2.45 s			2.45 s	
Ph				7.35 d			7.35 d	
Ph				7.80 d			7.79 d	
MeO	3.33 s	3.33 s						
CMe_2			1.37 s	1.30 s	1.36 s	1.36 s	1.34 s	1.36 s
CMe_2			1.43 s	1.34 s	1.41 s	1.41 s	1.39 s	1.41 s
$J_{H,H}$								
1a,1b			7.9	8.1	8.0		10.0	6.8
1a,2	5.5	5.6	6.3	6.0	6.1			7.2
1b,2			7.4	6.7	6.0	6.8		
2,3			6.5		6.0	6.0		7.4
3,4	6.5		6.0					
4,5		7.0	4.5					
5,6						6.2		6.8
Ph				8.7			8.4	

[a] $CDCl_3$ (internal Me_4Si).

TABLE III

^{1}H-N.M.R. DATA[a] (250 MHz)

Proton	*Compound*								
	6	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
H-1	4.80 d	4.80 d	4.81 d	4.80 d	4.75 d	4.77 d	4.74 d	4.78 d	4.74 d
H-2	5.06 dd	5.04 dd	5.05 dd	5.04 dd	5.04 dd	5.04 dd	5.03 dd	5.03 dd	5.03 dd
H-3	5.24 t	5.23 t	5.23 t	5.23 t	5.22 t	5.23 t	5.22 t	5.22 t	5.22 t
H-4	5.06 t	5.08 t	5.07 t	5.09 t	5.06 t	5.09 t	5.07 t	5.08 t	5.07 t
H-5	3.73 ddd	3.73 ddd	3.74 dt	3.73 ddd	3.73 dt	3.72 ddd	3.72 dt	3.71 ddd	3.72 dt
H-6a	4.20 dd	4.25 dd	4.18 d	4.23 dd	4.17 d	4.24 dd	4.18 d	4.22 dd	4.18 d
H-6b	4.15 dd	4.14 dd		4.16 dd		4.14 dd		4.14 dd	
H-1′	4.78 t	4.90 dd	4.69 t	4.83 dd	4.70 t	4.85 t	4.60 t	4.79 t	4.59 t
H-2′a	3.40 d	3.42 dd	3.39 dd	3.38 dd	1.74–2.01 m	1.92 dt	1.74–1.86 m	1.74–1.87 m	1.60–1.79 m
H-2′b		3.37 dd	3.29 dd	3.25 dd		1.91 dt			
H-3′					3.38 t	3.39 t	1.93 tt	1.94 tt	1.60–1.79 m
H-4′							3.41 t	3.43 t	3.29 t
H-5′									
H-N									
MeO	3.45 s	3.41 s	3.46 s	3.44 s	3.41 s	3.35 s	3.39 s	3.32 s	3.39 s
OAc	2.02 s	2.02 s	2.01 s	2.01 s	2.02 s	2.01 s	2.02 s	2.01 s	2.01 s
	2.04 s	2.04 s	2.05 s	2.04 s	2.04 s	2.04 s	2.04 s	2.03 s	2.04 s
	2.06 s	2.06 s	2.06 s	2.06 s	2.06 s	2.06 s	2.06 s	2.05 s	2.05 s
	2.08 s	2.10 s	2.08 s	2.09 s	2.08 s	2.09 s	2.08 s	2.09 s	2.08 s
$J_{H,H}$									
1,2	8.3	8.0	8.1	7.9	8.0	8.0	7.9	8.1	7.8
2,3	9.5	9.8	9.5	9.4	9.5	9.5	9.5	9.5	9.6
3,4	9.5	9.8	9.5	9.4	9.5	9.5	9.2	9.5	9.6
4,5	9.8	9.8	10.0	9.4	9.5	9.5	9.5	9.5	9.6
5,6a	5.0	5.3	4.1	4.8	4.2	5.0	3.8	5.0	3.9
5,6b	3.3	2.5		2.7		2.7		2.7	
6a,6b	12.3	12.4		12.3		12.4		12.3	
1′,2′a	5.5	4.5	5.9	6.4	6.0	5.6	5.3	5.4	5.3
1′,2′b		6.8	4.8	4.1					
2′a,2′b		11.3	13.0	13.1					
2′,3′					3.3	6.9			
3′,4′							6.6	6.6	6.5
4′,5′									

Proton	*Compound*							
	15	**16**	**17**	**18**	**19**	**20** R S	**21** R S	**22** R S
H-1	4.78 d	4.63 d	4.71 d	4.59 d	4.69 d	4.58 d/4.68 d	4.57 d/4.68 d	4.56 d/4.67 d
H-2	5.03 dd	3.31 t	3.34 t	3.29 t	3.32 t	3.24–3.55 m	3.30 dd	3.24–3.55 m
H-3	5.22 t	3.37–3.52 m	3.35–3.56 m	3.36–3.55 m	3.35–3.55 m	3.24–3.55 m	3.37–3.55 m	3.24–3.55 m
H-4	5.08 t	3.37–3.52 m	3.35–3.56 m	3.36–3.55 m	3.35–3.55 m	3.24–3.55 m	3.37–3.55 m	3.24–3.55 m
H-5	3.71 ddd	3.37–3.52 m	3.35–3.56 m	3.36–3.55 m	3.35–3.55 m	3.24–3.55 m	3.37–3.55 m	3.24–3.55 m
H-6a	4.23 dd	3.91 dd	3.91 dd	3.91 dd	3.91 dd	3.91 dd	3.89 dd	3.90 dd
H-6b	4.14 dd	3.74 dd	3.71 dd	3.74 dd	3.71 dd	3.71 dd	3.71 dd	3.70 dd
H-1′	4.78 t	4.90 t	5.03 t	4.88 t	5.02 t	4.95 t	4.93 dd	4.92 t
H-2′a	1.59–1.79 m	3.37–3.52 m	3.35–3.56 m	1.98 p	1.98 p	1.62–1.84 m	1.44–1.77 m	1.56–1.78 m
H-2′b								
H-3′	1.59–1.79 m			3.36–3.55 m	3.35–3.55 m	1.62–1.84 m	1.44–1.77 m	1.46 q
H-4′	3.30 t					3.24–3.55 m	3.19 t	1.56–1.78 m
H-5′								3.24–3.55 m
H-N								
MeO	3.32 s	3.54 s	3.52 s	3.50 s	3.46 s	3.50 s/3.44 s	3.43 s	3.47/3.43
OAc	2.01 s						1.97 s	
	2.04 s							
	2.06 s							
	2.09 s							
$J_{H,H}$								
1,2	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
2,3	9.6	8.0	9.0	8.8	9.0		9.0	
3,4	9.6							
4,5	9.6							
5,6a	4.8	1.2	1.9	1.5	1.9	1.5	2.1	1.4
5,6b	2.7	4.6	5.4	4.9	5.2	5.3	5.4	5.6
6a,6b	12.3	12.5	12.3	12.3	12.3	12.3	12.3	12.3
1′,2′a	4.7	4.6	5.0	5.8	5.6	5.3	5.4	6.0
1′,2′b								
2′a,2′b								
2′,3′				6.0	6.7			
3′,4′	6.6					5.3	6.8	
4′,5′								

Table III (continued)

Proton	*Compound*							
	23	**24**	**25** R S	**26** R S	**35**	**36**	**37** R S	**38** R S
H-1	4.62 d	4.71 d	4.57 d/4.68 d	4.57 d/4.67 d	4.55 d	4.84 d	4.77 d	4.74 d/4.79 d
H-2	3.31 t	3.33 dd	3.30 t	3.27 dd	3.24 dd	3.33 dd	5.02 dd	5.03 dd
H-3	3.38–3.54 m	3.35–3.56 m	3.36–3.55 m	3.32–3.55 m	5.19 t	5.24 dd	5.23 t	5.22 t
H-4	3.38–3.54 m	3.35–3.56 m	3.36–3.55 m	3.32–3.55 m	5.11 t	5.09 t	5.09 t	5.09 t
H-5	3.38–3.54 m	3.35–3.56 m	3.36–3.55 m	3.32–3.55 m	3.85 ddd	3.84 ddd	3.70 dt	3.70 ddd
H-6a	3.90 dd	3.91 d	3.90 dd	3.90 dd	4.25 dd	4.26 d	4.21 d	4.17 d/4.24 dd
H-6b	3.74 dd	3.71 dd	3.70 dd	3.70 dd	4.18 dd	4.17 dd		/4.14 dd
H-1′	4.74 t	5.01 t	4.93 t	4.92 t	4.76 dd	4.77 d	4.76 t	4.57 t/4.77 t
H-2′a	2.79 d	1.99 q	1.72 m	1.72 m	3.87 dd	3.87 d	1.51–1.71 m	1.35–1.73 m
H-2′b					3.31 dd	3.71 dd		
H-3′		2.98 t	1.53 p	1.34–1.59 m			1.51–1.71 m	1.35–1.73 m
H-4′			2.67 t	1.34–1.59 m			3.25 o	1.35–1.73 m
H-5′				2.71 t				3.28 t
H-N							5.86 s	
MeO	3.51 s	3.47 s	3.48 s/3.43 s	3.47 s/3.43 s	3.56 s	3.51 s	3.38 s/3.31 s	3.38 s/3.31 s
OAc					2.04 s	2.04 s	1.99 s	2.01 s
					2.07 s	2.06 s	2.01 s	2.04 s
					2.09 s	2.09 s	2.04 s	2.05 s
							2.06 s	2.07 s/2.09 s
							2.09 s	
$J_{H,H}$								
1,2	8.0	7.8	8.0	8.0	7.5	8.0	8.0	8.0/8.2
2,3	8.4	9.5	9.0	9.5	9.5	10.1	9.5	9.3
3,4					9.5	9.0	9.5	9.3
4,5					9.0	9.8	10.0	9.5
5,6a	1.5		1.7	1.7	4.5	4.5	3.6	3.8/5.0
5,6b	4.6	5.3	5.3	5.3	2.7	2.7		/2.7
6a,6b	12.3	12.3	12.4	12.4	12.6	12.5		/12.3
1′,2′a	5.7	5.3	5.5	5.5	2.9		5.1	5.6
1′,2′b					9.0	2.0		
2′a.2′b					12.8	12.3		
2′,3′		6.0						
3′,4′			7.1				6.8	
4′,5′				7.1				6.8

[a]$CDCl_3$ (internal Me_4Si) and for compounds **16–26** D_2O (DSS as standard).

same upfield or downfield shift. Likewise, the optical rotations of the acetylated tentative "*R*-isomers", in comparison with the "*S*-isomers", have the smaller negative values. This order is reversed in the deacetylated pairs.

In preliminary experiments, the compounds (*R*)-2-azido-1-methoxyethyl β-D-glucopyranoside (**16**), (*S*)-2-azido-1-methoxyethyl β-D-glucopyranoside (**17**), (*R*)-3-azido-1-methoxypropyl β-D-glucopyranoside (**18**), (*S*)-3-azido-1-methoxypropyl β-D-glucopyranoside (**19**), (*R,S*)-4-azido-1-methoxybutyl β-D-glucopyranoside (**20**), (*R,S*)-4-acetamido-1-methoxybutyl β-D-glucopyranoside (**21**), and (*R,S*)-5-azido-1-methoxypentyl β-D-glucopyranoside (**22**) all underwent cleavage by the β-D-glucosidase from sweet almonds. Semiquantitative rate-measurements showed that the "*R*-isomer" **16** is hydrolyzed about five times faster than the "*S*-isomer" **17**, pointing to an apparent coincidence between hydrolysis rate and thermodynamic stability. Although not stringent for kinetically controlled reactions, it is reasonable to claim that the less-stable isomer should be hydrolyzed faster but be formed during synthesis at a lower rate. The same observation was made with 1-methoxyalkyl α-D-glucopyranosides[1,2]. Judging from molecular models of the most stable conformation, mainly controlled by the anomeric effect, in fact the "*S*-isomers" of the β-D-glucosides must be more stable because they lack the unfavourable interaction between the ring-oxygen atom and the bulky substituted-alkyl group. This order is reversed in the corresponding α-D-glucosides.

The azido derivatives **16, 19, 20,** and **22** could, without difficulty, be converted by catalytic hydrogenation into the corresponding ω-amino-1-methoxyalkyl β-D-glucopyranosides, (*R*)-2-amino-1-methoxyethyl β-D-glucopyranoside (**23**), (*S*)-3-amino-1-methoxypropyl β-D-glucopyranoside (**24**), (*R,S*)-4-amino-1-methoxybutyl β-D-glucopyranoside (**25**), and (*R,S*)-5-amino-1-methoxypentyl β-D-glucopyranoside (**26**). Preliminary tests showed that the amines could not be hydrolyzed by β-D-glucosidase under the same conditions that brought about complete hydrolysis of the neutral azides or the *N*-acetylated amine **21**. With increased enzyme concentration and incubation time, very slow hydrolysis of the amines (except for compound **24**) could be observed. Exact determination of kinetic parameters of the interaction of the amines with β-D-glucosidase from sweet almonds is under way.

CORRECTIONS

In ref. 10, the ^{1}H-n.m.r. signals for H-1 and H-3 in 3-azido-1-methoxybutyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**7**) were interchanged and the H-4 should be 5.06 instead of 4.06. Table II has the corrected values. Also the tentative statement[10] that the major diastereomeric component has the *R*-configuration at the acetal carbon must be reversed.

EXPERIMENTAL

Methods. — All reactions were monitored by t.l.c. on silica gel 60 F_{254} (Merck) using the solvents: *A* (1:1 EtOAc–light petroleum), *B* (1:2 EtOAc–light petroleum), *C* (5:1 EtOAc–MeOH), *D* (7:2:1 EtOAc–MeOH–H_2O) or *E* (7:3:3:2:3:2 1-propanol–EtOH–EtOAc–C_5H_5N–H_2O–AcOH. Solutions were evaporated *in vacuo*. Preparative column chromatography was performed on silica gel 60 (0.063–0.2 mm, Merck) using the "flash" technique[9] I.r. spectra were obtained with a Perkin–Elmer 1320 spectrophotometer. Optical rotations were measured with a Perkin–Elmer 141 polarimeter using $CHCl_3$ for acetylated and EtOH for deacetylated compounds. Melting points are uncorrected. ^{1}H-N.m.r. spectra were recorded with a Bruker WM 250 spectrometer at 250 MHz in $CDCl_3$ (internal Me_4Si) or D_2O [internal sodium 4,4-dimethyl-4-silapentane-1-sulphonate (DSS)]. Light petroleum refers to the fraction b.p. 60–70°.

Enzymic reactions. — β-D-Glucosidase (β-D-glucoside glucohydrolase, EC 3.2.1.21) from sweet almonds was purchased from Boehringer Mannheim. The enzymic reactions were performed in 0.1M sodium potassium phosphate buffer (pH 6.8) at 25°. Substrate concentrations were 30mM and enzyme concentrations were 0.4 mg/mL. Products were analysed semiquantitatively by t.l.c. on silica gel 60 (solvent *E*) with a Vitatron Densitometer TLD 100.

1,2-O-Isopropylidene-4-butanetriol (**27**). — 1,2,4-Butanetriol (30.0 g, 283 mmol) was stirred in Me_2CO (500 mL) with anhydrous $CuSO_4$ (30 g) and conc. H_2SO_4 (300 μL). After 2 h, concentrated aq. NH_4OH (10 mL) was added and the deep-blue precipitate was filtered off. The filtrate was evaporated and the residue was taken up in CH_2Cl_2 (100 mL), washed with saturated aq. $NaHCO_3$ (75 mL) and water (2 × 75 mL), dried ($MgSO_4$), and evaporated. Distillation under diminished pressure gave **27** (28 g, 68%); b.p. 97° (12 Torr); R_F 0.16 (solvent *A*); ν_{max}^{film} 1380 d (CMe_2), 3100–3600 cm^{-1} (OH); for n.m.r. data see Table II.

1,2-O-Isopropylidene-4-butanetriol p-*toluenesulphonate* (**28**). — Compound **27** (26 g, 178 mmol) in C_5H_5N (500 mL) was treated under stirring with an excess of TsCl (55 g, 285 mmol). After 2 h, ice (200 g) was added to the mixture, and 1 h later the mixture was diluted with water (1 L) and extracted with CH_2Cl_2 (500 mL). The organic layer was washed with saturated aq. $NaHCO_3$ (400 mL) and water (2 × 300 mL), dried ($MgSO_4$), and evaporated to yield compound **28** as an oil (44 g, 80%); R_F 0.50 (solvent *A*); for n.m.r. data see Table II.

4-Azido-1,2-O-isopropylidenebutanediol (**29**). — Compound **28** (40 g, 130 mmol) in dry Me_2SO (500 mL) was stirred with an excess of NaN_3 (50 g, 770 mmol) for 2 h at 80°. The cooled mixture was poured into Me_2CO (1 L) under stirring, the precipitate was filtered off, and the filtrate was evaporated. The residue, mainly Me_2SO, was taken up in water (1 L) and extracted with Et_2O (5 × 200 mL). The combined extracts were washed with water (3 × 100 mL), dried ($MgSO_4$), and evaporated under diminished pressure to yield **29** (19.0 g, 85%); R_F 0.59 (solvent *A*); ν_{max}^{film} 2090 (N_3), 1350 cm^{-1} (CMe_2); for ^{1}H-n.m.r. data see Table II.

3-Azidopropanal (**30**). — Compound **29** (21.0 g, 123 mmol) was stirred in aq.

AcOH (200 mL, 25%) for 2 h at 60°. Formation of the diol was monitored by t.l.c. (R_F of diol 0.17, solvent *A*). The acidic solution was diluted with water (100 mL) and stirred in the dark with $NaIO_4$ (35 g, 164 mmol). After 30 min the mixture was filtered and the filtrate extracted with CH_2Cl_2 (4 × 100 mL). The combined extracts were made neutral with saturated aq. $NaHCO_3$, washed with water (100 mL), dried ($MgSO_4$), and evaporated carefully under diminished pressure to yield the very volatile and reactive aldehyde **30** (11 g, incl. solvent); R_F 0.51 (solvent *A*); ν_{max}^{film} 1725 (C=O), 2100 cm^{-1} (N_3). For further identification, compound **30** was treated with 2,4-dinitrophenylhydrazine to yield the 2,4-dinitrophenylhydrazone, m.p. 128–130° (lit. 129–130°)[12].

3-Azidopropanal dimethyl acetal (**3**). — Compound **30** (10 g, with some solvent) was taken up in dry MeOH (200 mL) and stirred for 2 h with anhydrous $CuSO_4$ (15 g) and conc. H_2SO_4 (200 μL). After filtration, C_5H_5N (20 mL) was added to the filtrate and this mixture was evaporated at room temperature. The residue was taken up in solvent *A*. Inorganic material was removed by filtration through a silica gel bed and the solution was evaporated under diminished pressure. The residue was taken up in CH_2Cl_2 (100 mL), washed with sat. aq. $NaHCO_3$ (75 mL) and water (2 × 75 mL), dried ($MgSO_4$), and distilled *in vacuo* (12 Torr) to yield pure **3** (4 g), b.p. 62–70° (12 Torr); R_F 0.59 (solvent *A*); ν_{max}^{film} 2090 (N_3), 2840 cm^{-1} (OCH_3).

1,2-O-Isopropylidenehexane-1,2,6-triol (**31**). — 1,2,6-Hexanetriol (50 g, 373 mmol) was treated as described for 1,2,4-butanetriol to yield **31** (49.5 g, 76%); b.p. 69° (0.5 Torr); R_F 0.29 (solvent *C*); ν_{max}^{film} 3100–3600 (OH), 1380 cm^{-1} d(CMe_2); ^{1}H-n.m.r. data see Table II.

1,2-O-Isopropylidenehexane-1,2,6-triol 6-p-toluenesulphonate (**32**). — Compound **31** (40 g, 230 mmol) was treated as described for **27** to yield **32** (58 g, 75%); R_F 0.48 (solvent *A*); ^{1}H-n.m.r. data see Table II.

6-Azido-1,2-O-isopropylidene-hexane-1,2-diol (**33**). — Compound **32** (57 g, 173 mmol) was treated as described for **28** to give **33** (25.5 g, 74%); R_F 0.62 (solvent *A*); ν_{max}^{film} 2090 (N_3), 1350 cm^{-1} d(CMe_2); ^{1}H-n.m.r. data see Table II.

5-Azidopentanal (**34**). — Compound **33** (12 g, 60 mmol) was treated as described for **29** with AcOH and subsequently with $NaIO_4$ (18 g, 84 mmol) to yield **34** (9 g, incl. solvent); R_F 0.62 (solvent *A*). For further identification, compound **34** was treated with 2,4-dinitrophenylhydrazine to yield the 2,4-dinitrophenylhydrazone, m.p. 64–65° (ethanol).

Anal. Calc. for $C_{11}H_{17}N_7O_4$: C, 43.00; H, 4.26; N, 31.91. Found: C, 43.03; H, 4.35; N, 32.12.

5-Azidopentanal dimethyl acetal (**5**). — Compound **34** (9 g, incl. solvent) was treated as described for **30** to yield **5** (6.3 g); b.p. 71–77° (0.3 Torr); ν_{max}^{film} 2090 (N_3), 2830 cm^{-1} (OCH_3); ^{1}H-n.m.r. data see Table II.

4-Bromobutanal dimethyl acetal (**4**). — 4-Bromobutanal was prepared from tetrahydrofuran with HBr and subsequent oxidation with pyridinium chlorochromate[11]. The acetalation of 4-bromobutanal (15 g, 100 mmol) was carried out as

already described for **3** to give **4** (10 g, 51%); b.p. 48–53° (1 Torr); R_F 0.47 (solvent *B*); ν_{max}^{film} 2840 cm^{-1} (OCH_3); ^{1}H-n.m.r. data see Table II.

(R)-*2-Bromo-1-methoxyethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside* (**6**) *and* (S)-*2-bromo-1-methoxyethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside* (**7**). — To 2,3,4,6-tetra-*O*-acetyl-1-*O*-trimethylsilyl-β-D-glucose (**1**, 4.5 g, 10.7 mmol) in dry CH_2Cl_2 (25 mL) was added 2-bromoacetaldehyde dimethyl acetal (**2**) (12 mL, 49 mmol) and trimethylsilyl triflate (3 mL, 0.55M) at −78°. After 48 h, Et_3N (20 mL) was added and the mixture was warmed to room temperature, washed with saturated aq. $NaHCO_3$ (3 × 20 mL), aq. NaCl (3 × 20 mL), dried (Na_2CO_3, Na_2SO_4) and evaporated. The residue was purified by flash chromatography[12] (2:5 EtOAc–light petroleum) and separated into the diastereomeric isomers by flash chromatography (1:5 EtOAc–light petroleum) to yield initially compound **6** (285 mg, 5.5%) m.p. 92° (EtOAc–light petroleum); for further data see Tables I and III.

Anal. Calc. for $C_{17}H_{25}BrO_{11}$: C, 42.08; H, 5.19; Br, 16.46. Found: C, 42.24; H, 5.26; Br, 16.47.

Next eluted was compound **7** (334 mg, 6.4%), m.p. 123° (EtOAc–light petroleum); for further data see Table I and III.

Anal. Calc. for $C_{17}H_{25}BrO_{11}$: C, 42.08; H, 5.19; Br, 16.46. Found: C, 41.90; H, 5.45; Br, 16.33.

(R)-*2-Azido-1-methoxyethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside* (**8**). — Compound **6** (220 mg, 453 μmol) in dry Me_2SO (5 mL) was stirred with NaN_3 (300 mg, 4.6 mmol) at 80°. After 6 h, the mixture was cooled to room temperature, poured into Me_2CO (100 mL), and the inorganic salts were filtered off. The filtrate was evaporated, the residue taken up in water (100 mL), and extracted with ether (4 × 50 mL). The extracts were washed with water (2 × 100 mL), dried ($MgSO_4$), and evaporated under diminished pressure to yield **8** (170 mg, 86%), m.p. 101.5° (Et_2O–petroleum ether b.p. 30–50°); ν_{max}^{KBr} 2110 cm^{-1} (N_3); for further data see Tables I and III.

Anal. Calc. for $C_{17}H_{25}N_3O_{11}$: C, 45.64; H, 5.63; N, 9.39. Found: C, 45.76; H, 5.81; N, 9.59.

(S)-*2-Azido-1-methoxyethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside* (**9**). — Compound **7** (260 mg, 536 μmol) was treated as described for compound **6** to give **9** (190 mg, 80%) m.p. 94° (Et_2O–petroleum ether, b.p. 30–50°); ν_{max}^{KBr} 2110 cm^{-1} (N_3); for further data see Tables I and III.

Anal. Calc. for $C_{17}H_{25}N_3O_{11}$: C, 45.64; H, 5.63; N, 9.39. Found: C, 45.80; H, 5.79; N, 9.59.

(R)-*2-Azido-1-methoxyethyl β-D-glucopyranoside* (**16**). — Compound **8** (414 mg, 925 μmol) was deacetylated by the Zemplén method to give **16** (201 mg, 78%), m.p. 135–136° dec. (Me_2CO); R_F 0.51 (solvent *D*); ν_{max}^{KBr} 2100 cm^{-1} (N_3); for further data see Tables I and III.

Anal. Calc. for $C_9H_{17}N_3O_7$: C, 38.63; H, 6.13; N, 15.04. Found: C, 38.63; H, 6.10; N, 14.82.

(S)-*2-Azido-1-methoxyethyl β-D-glucopyranoside* (**17**). — Compound **9** (390

mg, 872 μmol) was treated as described for **8** to give syrupy **17** (242 mg); R_F 0.51 (solvent *D*); ν_{max}^{film} 2100 cm^{-1} (N_3); for further data see Tables I and III.

(R)-*2-Amino-1-methoxyethyl β-D-glucopyranoside* (**23**). — A solution of compound **16** (139 mg, 498 μmol) in EtOH (20 mL) was hydrogenated in the presence of Adams' catalyst (~20 mg PtO_2) for 2 h. Platinum was filtered off and the filtrate was evaporated to yield **23** (85 mg, 67%), m.p. 164–166° (EtOH), $[\alpha]_D^{23}$ −49.0° (*c* 1.0, EtOH); R_F 0.40 (solvent *E*); ν_{max}^{KBr} 1580 cm^{-1} (NH_2); ^{1}H-n.m.r. data, see Table III.

Anal. Calc. for $C_9H_{19}NO_7$: C, 42.68; H, 7.56; N, 5.53. Found: C, 42.62; H, 7.58; N, 5.49.

(6R)-6-Methoxy-(3,4,6-tri-O-acetyl-β-D-glucopyrano)[1,2-b]-1,4-dioxane (**35**). — Compound **6** (80 mg, 165 μmol) was deacetylated by the Zemplén method and the solution evaporated. The solid residue was dissolved in *tert*-butanol (10 mL), $KOBu^t$ (40 mg) was added, and the mixture was stirred for 12 h at 40°. After evaporation of the solvent the residue was acetylated in C_5H_5N (5 mL) and Ac_2O (3 mL) for several h (t.l.c.) followed by conventional processing. Purification was carried out by flash chromatography (solvent *B*) to yield the syrupy compound **35** (36 mg, 60%), R_F 0.39 (solvent *A*); for ^{1}H-n.m.r. data see Table III.

(6S)-6-Methoxy-(3,4,6-tri-O-acetyl-β-D-glucopyrano)[1,2-b]-1,4-dioxane (**36**). — Compound **7** (94 mg, 194 μmol) was treated as described for compound **6** to yield **36** as a syrup (40 mg, 57%), R_F 0.32 (solvent *A*); for ^{1}H-n.m.r. data see Table III.

(R)-*3-Azido-1-methoxypropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside* (**10**) *and* (S)-*3-azido-1-methoxypropyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside* (**11**). — Compound **1** (1.5 g, 3.57 mmol) and compound **3** (1 mL, 7.1 mmol) were treated as described for **1** and **2** to yield the diastereomeric isomers **10** and **11**. Data for compound **10** (125 mg, 7.6%); m.p. 60° (Et_2O–petroleum ether, b.p. 30–50°); ν_{max}^{KBr} 2090 cm^{-1} (N_3); for further data see Tables I and III.

Anal. Calc. for $C_{18}H_{27}N_3O_{11}$: C, 46.85; H, 5.90; N, 9.11. Found: C, 46.91; H, 6.12; N, 9.07.

Data for compound **11** (236 mg, 14.4%); m.p. 73° (Et_2O–petroleum ether, b.p. 30–50°), ν_{max}^{KBr} 2090 cm^{-1} (N_3); for further data see Tables I and III.

Anal. Calc. for $C_{18}H_{27}N_3O_{11}$: C, 46.85; H, 5.90; N, 9.11. Found: C, 46.92; H, 6.11; N, 9.11.

(R)-*3-Azido-1-methoxypropyl β-D-glucopyranoside* (**18**). — Compound **10** (200 mg, 433 μmol) was deacetylated by the Zemplén method to give **18** (53 mg, 42%), m.p. 155–156° (acetone); R_F 0.53 (solvent *D*); ν_{max}^{KBr} 2100 cm^{-1} (N_3); for further data see Tables I and III.

Anal. Calc. for $C_{10}H_{19}N_3O_7$: C, 40.95; H, 6.53; N, 14.33. Found: C, 41.22; H, 6.35; N, 14.38.

(S)-*3-Azido-1-methoxypropyl β-D-glucopyranoside* (**19**). — Compound **11** (480 mg, 1.04 mmol) was deacetylated by the Zemplén method to give **19** (248 mg, 81%), m.p. 96–97° (acetone); R_F 0.53 (solvent *D*); ν_{max}^{KBr} 2100 cm^{-1} (N_3); for further data see Tables I and III.

Anal. Calc. for $C_{10}H_{19}N_3O_7$: C, 40.95; H, 6.53; N, 14.33. Found: C, 40.70; H, 6.54; N, 14.62.

(S)-*3-Amino-1-methoxypropyl β-*D*-glucopyranoside* (**24**). — Compound **19** (235 mg, 805 μmol) was dissolved in EtOH (30 mL) and hydrogenated as described for compound **16** to yield **24** (216 mg, syrup); R_F 0.42 (solvent *E*), $[\alpha]_D^{23}$ −24.0° (*c* 1.0, water); ν_{max}^{film} 1580 cm^{-1} (NH_2); for ^{1}H-n.m.r. data see Table III.

(R)-*4-Bromo-1-methoxybutyl 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranoside* (**12**) *and* (S)-*4-bromo-1-methoxybutyl 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranoside* (**13**). — Compound **1** (4.5 g, 10.7 mmol) and compound **4** (6.4 mL, 40.6 mmol) were treated as described for **1** and **2** to yield the diastereomeric isomers **12** and **13**, which could not be separated completely; yield: 4.2 g (76%), m.p. 76–79° (Et_2O–petroleum ether, b.p. 30–50°); for further data see Tables I and III.

(R)-*4-Azido-1-methoxybutyl 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranoside* (**14**) *and* (S)-*4-azido-1-methoxybutyl 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranoside* (**15**). — The diastereomeric mixture of **12** and **13** (3.5 g, 6.8 mmol) in dry Me_2SO (50 mL) was treated with NaN_3 (4.5 g, 69.2 mmol) as described for **6** and **7** to yield the diastereomers **14** and **15** (3.15 g, 97%). A small portion of the isomeric mixture was separated by column chromatography (1:5 EtOAc–petroleum ether) for analytical use.

Data for **14**: m.p. 73–74° (Et_2O–petroleum ether, b.p. 30–50°); ν_{max}^{KBr} 2090 cm^{-1} (N_3); for further data see Tables I and III.

Anal. Calc. for $C_{19}H_{29}N_3O_{11}$: C, 48.00; H, 6.15; N, 8.84. Found: C, 48.27; H, 6.32; N, 8.67.

Data for **15**: m.p. 64–65° (Et_2O–petroleum ether, b.p. 30–50°); ν_{max}^{KBr} 2090 cm^{-1} (N_3); for further data see Tables I and III.

Anal. Calc. for $C_{19}H_{29}N_3O_{11}$: C, 48.00; H, 6.15; N, 8.84. Found: C, 47.93; H, 6.23; N, 8.73.

(R,S)-*4-Azido-1-methoxybutyl β-*D*-glucopyranoside* (**20**). — The diastereomeric mixture of compounds **14** and **15** (800 mg, 1.68 mmol) was deacetylated by the Zemplén method to yield **20**; m.p. 106–122° (Me_2CO); R_F 0.53 (solvent *D*); ν_{max}^{KBr} 2100 cm^{-1} (N_3); ^{1}H-n.m.r. data see Table III.

Anal. Calc. for $C_{11}H_{21}N_3O_7$: C, 42.99; H, 6.89; N, 13.67. Found: C, 42.78; H, 7.19; N, 13.89.

(R,S)-*4-Amino-1-methoxybutyl β-*D*-glucopyranoside* (**25**). — Compound **20** (335 mg, 1.09 mmol) in ethanol (30 mL) was treated as described for compound **16** to yield **25** as a syrup (310 mg); R_F 0.42 (solvent *E*); ν_{max}^{film} 1660 cm^{-1} (NH_2); ^{1}H-n.m.r. data see Table III.

(R,S)-*4-Acetamido-1-methoxybutyl 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranoside* (**37**). — Compound **25** (170 mg, 630 μmol) in pyridine (10 mL) was acetylated with Ac_2O (6 mL). After 4 h the mixture was processed conventionally and purified by column chromatography (solvent *C*) to yield **37** as a colourless syrup (235 mg); R_F 0.44 (solvent *C*); ν_{max}^{film} 1680 (amide I), 1560 cm^{-1} (amide II); ^{1}H-n.m.r. data see Table III.

(R,S)-*4-Acetamido-1-methoxybutyl β-D-glucopyranoside* (**21**). — Compound **37** (200 mg, 407 μmol) was deacetylated by the Zemplén method to yield compound **21** (132 mg, syrup); R_F 0.17 (solvent *D*); ν_{max}^{film} 1650 (amide I), 1560 cm^{-1} (amide II); ^{1}H-n.m.r. data, see Table III.

(R,S)-*5-Azido-1-methoxypentyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside* (**38**). — Compound **1** (3 g, 7.1 mmol) with compound **5** (4 g, 23.1 mmol) were treated as described for the reaction of **1** with **2** to yield **38** (1.4 g, 40%); m.p. 54–57° (Et_2O–petroleum ether, b.p. 30–50°); R_F 0.28 (solvent *A*); ν_{max}^{KBr} 2100 cm^{-1} (N_3); ^{1}H-n.m.r. data, see Table III.

Anal. Calc. for $C_{20}H_{31}N_3O_{11}$: C, 49.03; H, 6.38; N, 8.58. Found: C, 49.04; H, 6.43; N, 8.43.

(R,S)-*5-Azido-1-methoxypentyl β-D-glucopyranoside* (**22**). — Compound **20** (670 mg, 1.37 mmol) was deacetylated by the Zemplén method to give syrupy compound **22** (422 mg, 96%), R_F 0.53 (solvent *D*); ν_{max}^{film} 2100 cm^{-1} (N_3); ^{1}H-n.m.r. data, see Table III.

(R,S)-*5-Amino-1-methoxypentyl β-D-glucopyranoside* (**26**). — Compound **22** (382 mg, 1.09 mmol) dissolved in EtOH (30 mL) was treated as described for compound **16** to yield syrupy **26** (355 mg) R_F 0.43 (solvent *E*); ν_{max}^{film} 1600 cm^{-1} (NH_2); for ^{1}H-n.m.r. data see Table III.

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