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Note

Migration of a 1,2-*O*-benzylidene group under glycosylation conditions

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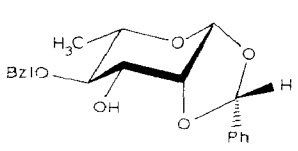
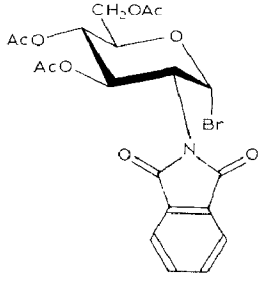
The benzylidene group is stable, as a rule, under glycosylation conditions, although some examples of migration are documented. Thus, Koenigs–Knorr glycosylation of benzyl 4,6-*O*-benzylidene-β-D-glucopyranoside by 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide is accompanied by migration of the benzylidene group and affords a branched trisaccharide with (1→3) and (1→6) linkages[1]. Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside behaves analogously[2,3]. However, direct evidence of the migration was lacking because the benzylidene group was absent from the trisaccharide derivatives obtained. We now report on the migration of the 1,2-*O*-benzylidene group in the rhamnose derivative **1** upon glycosylation.

Compound **1** was prepared[4] from 1,2-*O*-[(*R*)-benzylidene]-β-L-rhamnopyranose [isolated by crystallisation of an (*R*,*S*) mixture[5]] by sequential selective 3-benzoylation, 4-benzylation by benzyl trichloroacetimidate[6], and debenzoylation.



1



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Reaction of **1** with the glycosyl bromide **2**[7] in dichloromethane in the presence of silver triflate and 2,4,6-collidine afforded, after column chromatography, a 2–2.5:1 mixture (reversed-phase h.p.l.c. and ^{13}C-n.m.r. data) of 4-*O*-benzyl-1,2-*O*-benzylidene-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-β-L-rhamnopyranose and 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl 4-*O*-benzyl-2,3-*O*-benzylidene-β-L-rhamnopyranoside. Hydrazinolysis of the mixture followed by *N*,*O*-acetylation and column chromatography gave the major

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TABLE I

^{1}H-N.M R. DATA FOR **3–5** ($CDCl_3$, INTERNAL Me_4Si)

Compound	*GlcNAc*								*Rha*						*Other signals*			
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*NH*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*PhCH*	*PhCH$_2$*		*CH$_3$CO*
3	5.07	3.88	5.33	5.06	3.76	4.20	4.28	5.37	5.32	4.42	4.02	3.64	3.47	1.32	5.94	4.68	4.81	1.53; 1.99;
	d	m	dd	dd	m	dd	dd	d	d	dd	dd	t	m	d	s	d	d	2.03; 2.11
4	5.22	3.47	5.44	5.04	3.76	4.13	4.23	5.02	5.14	4.34	4.42	3.82	3.66	1.36	5.94	4.63	4.88	1.68; 2.01;
	d	m	dd	t	m	dd	dd	d	d	dd	dd	dd	m	d	s	d	d	2.02; 2.07
5	4.89	3.91	5.22	5.06	3.70	4.10	4.22	5.32	5.99	5.20	4.08	3.52	3.79	1.28	—	4.66	4.85	1.56; 2.00;
	d	m	dd	t	m	dd	dd	d	d	dd	dd	t	m	d		d	d	2.02; 2.08;
																		2.13; 2.14

Coupling constants (Hz)

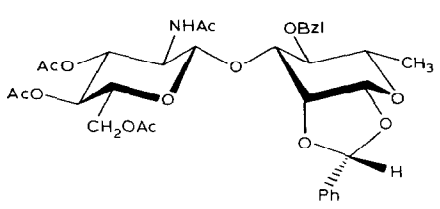
Compound	*GlcNAc*								*Rha*					$PhC\lessgtr^{H}_{H}$
	1,2	*2,3*	*3,4*	*4,5*	*5,6*	*5,6'*	*6,6'*	*NH,2*	*1,2*	*2,3*	*3,4*	*4,5*	*5,6*	
3	8.5	10.5	9	10	5	3	12	8.5	2	4	9.5	9.5	6	12
4	8.5	10.5	9.5	9.5	2.5	5	12	8.5	2.5	7.5	6.5	10	6.5	11.5
5	8.5	10.5	9.5	9.5	2.5	4.5	12.5	9	2	3.5	9.5	9.5	6	12

TABLE II

^{13}C-NMR DATA[a] FOR **3**, **4**, AND **6**

Compound	*GlcNAc*						*Rha*						*Other signals*		
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*PhCH*	*PhCH$_2$*	*CH$_3$CO*
3	102.0	55 4	72.5	69.0	72 05	62.3	96.2	81.0	80.7	79.25	71.1	18.1	106.5	74.8	20.6; 20.8; 22 9
4	98.8	55.9	72.2	69.0	72.05	62.4	96 75	74.9	79.95	79.9	71 1	19.3	104.35	72.85	20.6; 23.05
6	102.4	57.0	74.7	71.0	77 4	62.0	101.7	71.8	73.8	73.0	73.7	17 9	—	—	23.4

[a]Solutions in $CDCl_3$ (internal Me_4Si) for **3** and **4**; solution in D_2O (internal MeOH, δ 50.15) for **6**.



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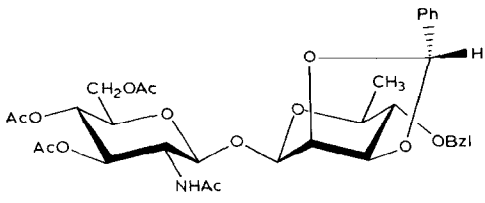
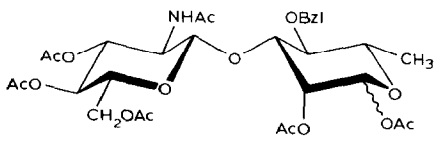


4

product which was shown by n.m.r. data (^{1}H and ^{13}C) and chemical transformations to be the expected, normal glycosylation product **3**.

The ^{1}H-n.m.r. spectrum of **3** contained, *inter alia,* signals for benzyl, benzylidene, and four acetyl groups (Table I). The $J_{1',2'}$ value* (8.5 Hz) indicated the interglycosidic bond to be β. This follows also from the chemical shift of the signal for C-1′ (Table II, signal assignments were made by selective heteronuclear ^{13}C{^{1}H} double-resonance). Debenzylidenation of **3** with aqueous 90% trifluoroacetic acid followed by acetylation gave **5**, the ^{1}H-n.m.r. spectrum of which contained, *inter alia,* signals for benzyl and six acetyl groups. The downfield shift of the signals for H-1 and H-2 compared to those in **3** indicated HO-1,2 of the rhamnose moiety to be acetylated and consequently that **3** contained a 1,2-*O*-benzylidene group, thus being a derivative of 3-*O*-(2-amino-2-deoxy-β-D-glucopyranosyl)-L-rhamnose.



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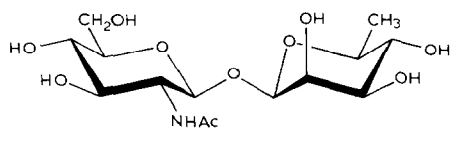

6

The ^{1}H-n.m.r. spectrum of the minor product **4** contained signals for benzyl, benzylidene, and four acetyl groups. That the 2-amino-2-deoxy-D-glucopyranosidic linkage was β was indicated by the $J_{1',2'}$ value (8.5 Hz) and the chemical shifts of the signals for C-3′ and C-5′ (Table II) (*cf.* ref. 8). Thus, **3** and **4** are not anomers. Attempted debenzylidenation of **4** with aqueous 90% trifluoroacetic acid resulted in formation of monosaccharide derivatives which, following acetylation, were identified by t.l.c. as 4-*O*-benzyl-L-rhamnose triacetate and 2-amino-2-deoxy-D-glucose penta-acetate. Deacetylation of **4** followed by hydrogenolysis gave the free disaccharide **6**.

The chemical shifts of the signals for C-2,3,4 of **6** indicated the absence of substituents at positions 2–4 (*cf.* ref. 8), and those of C-1 and C-1′ indicated the involvement of positions 1 and 1′ in the interglycosidic bond. The chemical shifts

*Primed numbers refer to the amino sugar moiety.

(δ 73.8 and 73.7) of the resonances for C-3,5 of the rhamnose moiety together with the absence of signals in the region of 69.5–70 p.p.m. characteristic for C-5 of α-L-rhamnosides[9] indicated the L-rhamnosidic bond to be β. Thus, **4** is a derivative of the non-reducing disaccharide 2-amino-2-deoxy-β-D-glucopyranosyl β-L-rhamnopyranoside with a 2,3-*O*-benzylidene group in the rhamnose moiety.

The configuration of the benzylidene group in **4** was assigned tentatively on the basis of a comparison of the ^{13}C-n.m.r. data with those for 2,3-*O*-benzylidene-α-L-rhamnosides[10], such data for β-L-rhamnosides being lacking. The chemical shift (104.35 p.p.m.) of the signal for the acetal carbon atom in **4** is in the region (103.9–104.7 p.p.m.) for the corresponding carbon atoms for methyl (and benzyl) 2,3-*O*-[(*R*)-benzylidene]-α-L-rhamnopyranosides (*endo*-benzylidene configuration); the acetal carbon atoms of *exo*-benzylidene derivatives resonate at <103.1 p.p.m. Another empirical rule also favours the *endo*-benzylidene configuration in **4**. Thus, the $\Delta\delta$ value for the quaternary (phenyl) and acetal carbon atoms of benzylidene groups is <33.7 p.p.m. for *endo*- and >35.4 p.p.m. for *exo*-benzylidene derivatives[10]; for **4**, $\Delta\delta$ was 32.85 p.p.m. (137.2–104.35).

Direct proof of the *endo*-benzylidene configuration in **4** was obtained from n.O.e. data. Saturation of the benzylidene acetal proton (δ 5.94) yielded differential n.O.e. (4%) of H-2,3 of the rhamnopyranosyl moiety.

Thus, glycosylation of **1** is accompanied by partial 1,2→2,3 migration of the benzylidene group. Retention of the β configuration of the rhamnose residue in **4** seems to indicate that it is O-1 in **1**, with fixed configuration of the glycosidic centre, that is subjected to glycosylation and not the rearranged 2,3-acetal having a hemiacetal hydroxyl group, which could be formed if migration preceded glycosylation.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer 141 polarimeter at 20 ±2°. N.m.r. spectra were recorded with a Bruker WM-250 spectrometer (250 MHz for ^{1}H and 62.89 MHz for ^{13}C spectra). T.l.c. was performed on Kieselgel 60 (Merck) and column chromatography on Silica Gel L (40–100 μm, CSSR) with a gradient of benzene → ethyl acetate. H.p.l.c. was performed on an Altex-332 instrument, with a UV-254 detector, and a column (5 μm, 25 ×0.46 cm) of Ultrasphere-ODS, using methanol–water (4:1) at 1.5 mL/min. Dichloromethane was washed with conc. H_2SO_4 and water, dried with $CaCl_2$, and distilled from CaH_2. Solutions were concentrated *in vacuo* at 40°.

Glycosylation of 4-O-benzyl-1,2-O-[(R)-benzylidene]-β-L-rhamnopyranose (**1**) *by 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-α-D-glucopyranosyl bromide* (**2**). — A mixture of **1** (1.71 g, 5 mmol), silver trifluoromethanesulphonate (2.06 g, 8 mmol), 2,4,6-collidine (1.15 mL, 8.7 mmol), and powdered molecular sieve 4A (2 g) in dichloromethane (20 mL) was stirred for 1.5 h at room temperature and then

cooled to −30°. A solution of **2** [obtained from 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-D-glucose[7] (8 mmol)] in dichloromethane (30 mL) was added dropwise during 1 h. The mixture was stirred for 1.5 h at −10 to −15° and then for 16 h at room temperature. The precipitate was collected and washed with chloroform (3 × 50 mL), and the combined filtrate and washings were washed with water (3 × 200 mL) and concentrated. Column chromatography of the residue gave a product (2.78 g, 73%), isolated as a colourless foam, R_F 0.54 (benzene–ethyl acetate 3:2). H.p.l.c. revealed two components (*T* 4.6 and 6 min) in the ratio ~2.5:1. ^{13}C-N.m.r. data ($CDCl_3$): major component, δ 106.4 (Ph*C*H), 99.7 (C-1′), 96.0 (C-1), 81.6, 80.8, 78.6, 74.5, 72.1, 71.0, 69.2 (C-2/5, C-3′/5′, Ph*C*H_2), 62.2 (C-6′), 54.9 (C-2′), and 17.9 (C-6); minor component, δ 104.6 (Ph*C*H), 97.0 (C-1′), 96.4 (C-1), 79.6, 79.4, 74.8, 72.6, 71.8, 71.2, 69.15 (C-2/5, C-3′/5′, Ph*C*H_2), 62.2 (C-6′), 54.7 (C-2′), and 18.6 (C-6).

3-O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-4-O-benzyl-1,2-O-benzylidene-β-L-rhamnopyranose (**3**) *and 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl 4-O-benzyl-2,3-O-benzylidene-β-L-rhamnopyranoside* (**4**). — The above mixture (2.78 g) was dissolved in ethanol (70 mL), hydrazine hydrate (1.5 mL) was added, and the mixture was boiled under reflux for 4 h and then cooled. The precipitate was collected and washed with ethanol (2 × 20 mL), the combined filtrate and washings were concentrated to dryness, and the residue was treated with acetic anhydride (10 mL) and pyridine (20 mL) at room temperature overnight. To the chilled (5–10°) solution was added methanol (5 mL), after 0.5 h the mixture was concentrated to half its volume, chloroform (200 mL) was added, and the solution was washed with water (3 × 200 mL) and concentrated. Column chromatography of the residue gave **3** (1.13 g), **4** (0.19 g), and a mixture of **3** and **4** (0.57 g); the total yield of **3** and **4** was 78%.

Compound **3** had m.p. 189–191° (from ethanol–ether, 1:5), $[\alpha]_D$ +47° (*c* 1.4, chloroform), R_F 0.24 (benzene–ethyl acetate 2:3).

Anal. Calc. for $C_{34}H_{41}NO_{13}$: C, 60.79; H, 6.15; N, 2.08. Found: C, 60.81; H, 6.15; N, 2.13.

Compound **4** had m.p. 216–217° (from methanol), $[\alpha]_D$ +29° (*c* 1.3, chloroform), R_F 0.15.

Anal. Found: C, 60.96; H, 6.26; N, 1.87.

3-O-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-1,2-di-O-acetyl-4-O-benzyl-L-rhamnopyranose (**5**). — To a solution of **3** (710 mg, 1.06 mmol) in chloroform (2 mL) was added aqueous 90% trifluoroacetic acid (4 mL), the mixture was kept for 40 min at room temperature and concentrated, and toluene–ethanol was distilled from the residue, which was then treated with acetic anhydride (3 mL) and pyridine (5 mL) overnight. Conventional work-up followed by chromatography yielded **5** (660 mg, 93%), m.p. 221–224° (from ethyl acetate–hexane), $[\alpha]_D$ −35° (*c* 1.4, chloroform), R_F 0.20 (benzene–ethyl acetate, 2:3).

Anal. Calc. for $C_{31}H_{41}NO_{15}$: C, 55.76; H, 6.19; N, 2.10. Found: C, 55.57; H, 5.98; N, 2.17.

Analogous treatment of **4** gave 1,2,3-tri-*O*-acetyl-4-*O*-benzyl-L-rhamnose (R_F 0.65) and 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-glucopyranose (R_F 0.10), which were identified by comparison with authentic samples by t.l.c. (benzene–ethyl acetate, 2:3).

2-Acetamido-2-deoxy-β-D-glucopyranosyl β-L-rhamnopyranoside (**6**). — To a suspension of **4** (135 mg, 0.2 mmol) in dry methanol (5 mL) was added methanolic M sodium methoxide (0.5 mL). The mixture became homogeneous in 30 min and crystallisation of the product occurred. After 30 min, methanol (5 mL) was added, the precipitate was dissolved by gentle warming, and the solution was neutralised with QU-2 (PyH^+) resin, filtered, and concentrated. A solution of the residue in aqueous 80% methanol (10 mL) was hydrogenolysed in the presence of 10% Pd/C (100 mg) for 6 h at 36°. The catalyst was collected and washed with aqueous 50% methanol, the combined filtrate and washings were concentrated, and the residue was crystallised from aqueous 90% methanol to give **6** (50 mg, 68%), m.p. 261–263° (dec.), $[\alpha]_D$ +22° (*c* 1, water).

Anal. Calc. for $C_{14}H_{25}NO_{10}$: C, 45.77; H, 6.86; N, 3.81. Found: C, 46.09; H, 6.95; N, 3.89.

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