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THE EFFECT OF REPLACING A 3-*O*-ACETYL GROUP BY A 3-*O*-BENZYL GROUP IN A METHYL 4-*O*-TRITYL-β-D-XYLOPYRANOSIDE DERIVATIVE ON THE EFFICIENCY OF 1,2-*trans*-GLYCOSYLATION WITH A D-XYLOSE 1,2-*O*-(1-CYANOETHYLIDENE) DERIVATIVE

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ABSTRACT

Replacement of AcO-3 in methyl 2,3-di-*O*-acetyl-4-*O*-trityl-β-D-xylopyranoside with a benzyl group greatly increases the 1,2-*trans*-stereoselectivity of glycosylation with a D-xylopyranose 1,2-*O*-(1-cyanoethylidene) derivative. Anomerisation of methyl 2-*O*-benzyl-β-D-xylopyranoside derivatives occurred under the action of triphenylmethylium perchlorate.

INTRODUCTION

In previous studies of triphenylmethylium perchlorate-catalyzed glycosylation of methyl 2,3-di-*O*-acetyl-4-*O*-trityl-β-D-xylopyranoside (**1**) with 1,2-*O*-(1-cyanoethylidene) derivatives of D-xylose and some other monosaccharides, the formation of 1,2-*cis*-linked disaccharide derivatives (10–30%) together with the desired, 1,2-*trans*-linked products was observed[1]. The loss of stereospecificity was suggested[2] to be connected with a decreased reactivity of the trityl ether **1**, steric factors, or competition by the catalyst counter-ion acting as a nucleophile. X-Ray analysis of **1** has revealed[3,4] a $^4C_1$ conformation with O-4 sterically shielded by the carbonyl oxygen of AcO-3, which should hinder attack of an electrophile at O-4.

Thus, it was of interest to investigate the stereochemical outcome of glycosylation of 4-*O*-tritylated methyl β-D-xylopyranoside derivatives having no carbonyl function in the 3-substituent, namely, methyl 2,3-di-*O*-benzyl- (**2**) and methyl 2-*O*-acetyl-3-*O*-benzyl-4-*O*-trityl-β-D-xylopyranosides (**3**) with 3,4-di-*O*-acetyl-1,2-*O*-[1-(*endo*-cyano)ethylidene]-α-D-xylopyranose (**6**).

RESULTS AND DISCUSSION

Compound **2** was prepared from methyl 2,3-di-*O*-acetyl-4-*O*-trityl-β-D-xylopyranoside[1] (**1**) by deacetylation and then benzylation. Treatment of methyl 2,3-anhydro-4-*O*-trityl-β-D-ribopyranoside[5] (**4**) with sodium benzyl oxide followed by acetylation gave **3** (65%) and methyl 3-*O*-acetyl-2-*O*-benzyl-4-*O*-trityl-β-D-arabino-

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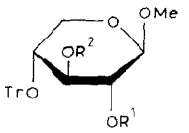

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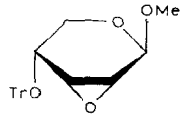

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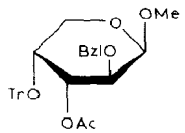

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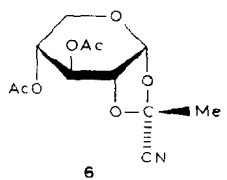

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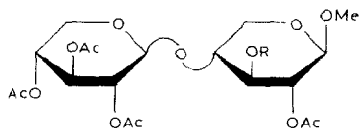

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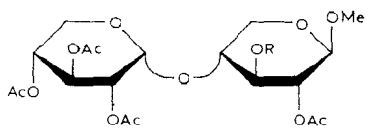

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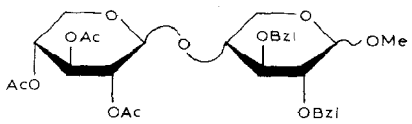

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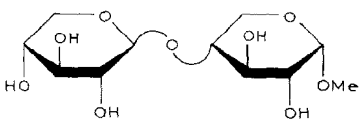

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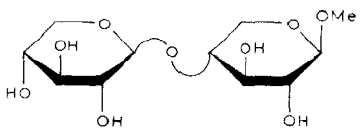

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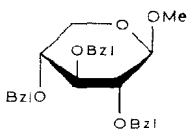

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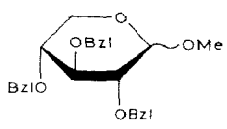

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pyranoside (**5**, 20%). The structure of **5** was established on the basis of ^{1}H-n.m.r. data (Table I). The ^3J values for **3** were smaller than those[1] for **1** and **2** (Table I). The products (**7** and **8**) of glycosylation of **3** (see below) had ^3J values typical of D-*xylo* compounds in the $^4C_1$ conformation. Thus, it follows that **3** is the derivative of methyl β-D-xylopyranoside and its conformation differs from $^4C_1$. The location of the acetyl and benzyl groups in **3** and **5** was indicated unequivocally by the chemical shifts of the resonances for H-2 and H-3 in ^{1}H-n.m.r. spectra.

Glycosylation of **3** with **6** was performed in the presence of 0.1 mol of triphenylmethylium perchlorate as a catalyst under conditions usually employed[1] for glycosylation with sugar 1,2-*O*-(1-cyanoethylidene) derivatives. The reaction proceeded as expected with high stereoselectivity and efficiency to give the disaccharide derivatives **7** and **8** (αβ-ratio 1:28) in a combined yield of 87%. An αβ-ratio of 1:2.1 was associated with the glycosylation[1] of **1** with **6** to give the disaccharide derivatives **9** and **10** in a similar combined yield.

In order to compare reactivities of the trityl ethers **1** and **3**, a mixture was glycosylated with **6** (molar ratio **6**:**1**:**3** = 1:1.1:1.1). The resulting mixture contained **1** and **3** together with four disaccharide derivatives (t.l.c.) from which **7** (76%) and **1** (70%) were isolated. Thus, **3** was more reactive than **1** and this may account for the higher stereoselectivity of its glycosylation.

The structure of the disaccharide derivatives **7** and **8** and the configuration of the newly formed linkages followed unequivocally from their ^{1}H- and ^{13}C-n.m.r. spectra (Tables I and II).

TABLE I

^{1}H-N.M.R. DATA ($CDCl_3$) (δ IN P.P.M., *J* IN Hz) FOR **2**, **3**, **5**, **7**, **8**, AND **14**

Compound	*Residue*[a]	*H-1*	*H-2*	*H-3*	*H-4*	*H-5a*	*H-5b*
2		4.32	3.41	3.90	3.78	2.95	2.81
3		4.40	4.84	3.45	3.67	2.94	3.27
5		4.80	4.23	5.07	3.94	2.88	3.29
7	R	4.26	4.86	3.54	3.84	3.22	3.98
	N	4.53	4.90	5.14	4.94	3.26	4.06
8	R	4.30	4.90	3.60	3.72	3.38	4.16
	N	5.15	4.87	5.51	4.98	3.67	3.85
14		4.38	3.48	[b]	3.33	[b]	4.06

$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5e}$	$J_{5a,5e}$
7.2	8.6	8.6	8.6	4.8	12.0
5.2	6.3	6.3	6.2	3.5	12.3
3.1	10.0	3.5	3.5	1.5	12.6
7.0	8.5	8.5	8.0	5.0	11.8
7.0	8.6	8.6	8.6	5.5	12.0
6.9	8.5	8.5	9.0	5.0	12.0
3.5	10.0	10.0	11.0	6.0	11.0
7.5	9.1			4.8	12.0

[a]R, "reducing" unit; N, "non-reducing" unit. [b]3.70 (m, 2 H, H-3,5*a*).

TABLE II

CHARACTERISTIC ^{13}C-N.M.R. DATA FOR **2, 3, 7, 11, 14**, AND **15** ($CDCl_3$; δ IN P.P.M., J IN Hz)

Compound	*Residue*[a]	*C-1*	*C-5*	*OCH_3*	$J_{C\text{-}1,H\text{-}1}$
2		104.9	64.6	56.6	
3		100.8	62.3	55.6	161
7	R	101.9	62.2	56.3	
	N	99.9	62.2		
11[b]	R	98.5	59.0	55.4	166
	N	99.6	61.6		160
11[c]	R	105.3	63.1	57.0	161
	N	99.9	62.1		159
14		105.1	63.6	56.5	161
15[b]		98.5	59.9	55.2	168
15[c]		105.4	64.0	56.7	

[a]R, "reducing" unit; N, "non-reducing" unit. [b]Major product. [c]Minor product.

Likewise, glycosylation of **2** with **6** was highly 1,2-*trans*-stereoselective. According to the ^{1}H-n.m.r. data, the mixture of products contained only traces of a compound with a non-reducing α-xylopyranosyl residue which could not be isolated. Analysis of the main product (**11**) by ^{13}C-n.m.r. spectroscopy showed it to be a 10:1 C-1 $\alpha\beta$-mixture (Table II). Hydrogenolysis of this product and deacetylation gave a mixture of methyl α- (**12**) and β-xylobiosides (**13**). The ^{13}C-n.m.r. spectrum of **13** (Table III) coincided with that reported[6]. The spectrum of **12** has not been reported hitherto and it was calculated from the ^{13}C-n.m.r. spectrum of methyl α-D-xylopyranoside, using spectral effects of glycosylation[6]. Coincidence of the experimental and calculated spectra of **12** is seen from the data in Table III.

The formation of the $\alpha\beta$-mixture **11** may have been due to triphenylmethylium perchlorate-induced anomerisation of the product **11β** and/or **2**. Anomerisation of glycosides in the presence of triphenylmethylium salts has not been observed previously. The possibility of anomerisation in the reaction of **2** and **6** was supported by the finding that treatment of methyl 2,3,4-tri-*O*-benzyl-β-D-

TABLE III

^{13}C-N.M.R. DATA FOR XYLOBIOSIDES **12** AND **13** (D_2O; δ IN P.P.M., J IN Hz)

Compound	*Residue*[a]	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*OCH_3*	$J_{C\text{-}1,H\text{-}1}$
12[b]	R	100.5	72.5	72.5	77.8	60.0	56.4	171
		(100.6)	(72.3)	(72.3)	(77.6)	(59.8)	(56.0)	
	N	103.1	74.0	76.9	70.4	66.5		160
		(103.1)	(74.0)	(76.9)	(70.4)	(66.5)		
13	R	105.1	74.0	75.0	77.7	64.1	58.4	156
	N	103.1	74.0	76.9	70.4	66.5		160

[a]R, "reducing" unit; N, "non-reducing" unit. [b]Calculated chemical shifts are given in parentheses.

xylopyranoside (**14**) with 0.1 mol of triphenylmethylium perchlorate under glycosylation conditions gave an 8.1:1 $\alpha\beta$-mixture of the xyloside **15** (^{13}C-n.m.r. data).

The anomerisation of **14** was accompanied by decomposition, which accounts for the relatively low yield (61%) of **15**. The yield of **11** was also rather low (51%) and was probably due to decomposition. Thus, the preparative use of this anomerisation reaction seems doubtful.

The increase in the stereoselectivity of glycosylation of **3** compared to that of **1** reflects the replacement of AcO-3 by a benzyl group and alteration of conformation (see above). However, comparison of the results of glycosylation of the trityl ethers **1** and **2**, which have the same conformation, shows that the presence of the benzyl group at O-3 results in higher stereoselectivity. This finding supplements the known approaches to the same end, *viz.*, the use of triphenylmethylium with complex anions (*e.g.*, tetrafluoroborate[2]) as catalysts and a high-pressure technique[7].

Sugar trityl ethers benzylated at O-2 should be avoided in glycosylations of the type discussed due to anomerisation and decomposition in the presence of triphenylmethylium perchlorate. This study supplements the previous report[8] where the formation of a complex mixture upon attempted glycosylation of methyl 2,4,6-tri-*O*-benzyl-3-*O*-trityl-α-D-galactopyranoside with a galactose 1,2-*O*-(1-cyanoethylidene) derivative was attributed to triphenylmethylium perchlorate-induced oxidation of BzlO-6.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and optical rotations, for solutions in chloroform, with a digital polarimeter DIP-360 (JASCO) at 30°. N.m.r. spectra were recorded with a Bruker WM-250 instrument for solutions in $CDCl_3$ (internal Me_4Si). Triphenylmethylium perchlorate was synthesised as described[9] and further purified by reprecipitation from nitromethane by the addition of ether[10]. Kieselgel 60 (Merck) was used for t.l.c. with ethyl acetate–toluene (*A*, 1:4; *B*, 1:3) and ethyl acetate–hexane (*C*, 7:33; *D*, 13:33), and detection by charring with sulphuric acid. Column chromatography was performed on Silica Gel L 40/100 μm (C.S.S.R.) by gradient elution with hexane–ethyl acetate (*E*) or benzene–ethyl acetate (*F*).

*Methyl 2,3-di-*O*-benzyl-4-*O*-trityl-β-*D*-xylopyranoside* (**2**). — To a solution of **1**[1] [1.0 g, 2.0 mmol; R_F 0.65 (solvent *A*)] in methanol (10 mL) was added methanolic M sodium methoxide (0.2 mL), and the mixture was kept for 20 min until deacetylation was complete (methyl 4-*O*-trityl-β-D-xylopyranoside has R_F 0.22), and then concentrated to dryness. To a solution of the residue in dry *N,N*-dimethylformamide (5 mL) was added sodium hydride (150 mg of an 80% dispersion in mineral oil; 5 mmol) followed by benzyl chloride (0.61 mL, 5 mmol) dropwise with cooling. The mixture was stirred for 1 h at 20°, then treated with methanol (5 mL), diluted with water (50 mL), and extracted with $CHCl_3$ (3 × 50 mL). The

combined extracts were washed with water and concentrated. Column chromatography of the residue (solvent *E*) gave amorphous **2** (0.95 g, 81%), $[\alpha]_D$ +22° (*c* 1), R_F 0.79 (solvent *A*) and 0.35 (solvent *B*).

The n.m.r. data are listed in Tables I and II.

Methyl 2-O-acetyl-3-O-benzyl-4-O-trityl-β-D-xylopyranoside (**3**) *and methyl 3-O-acetyl-2-O-benzyl-4-O-trityl-β-D-arabinopyranoside* (**5**). — To a solution of sodium benzyl oxide (from sodium hydride, 0.94 g of an 80% dispersion in mineral oil; 30 mmol) in benzyl alcohol (20 mL) was added a solution of **4**[5] (1.20 g, 3.1 mmol) [R_F 0.45 (solvent *D*)] in benzyl alcohol (10 mL). The mixture was heated for 20 h at 105° under dry argon until **4** disappeared (t.l.c.). Benzyl alcohol was distilled off and the residue was treated with acetic anhydride (15 mL) in pyridine (23 mL) in the presence of 4-dimethylaminopyridine (10 mg). Conventional work-up followed by column chromatography (solvent *E*) gave **3** (1.08 g, 64.7%) and **5** (0.34 g, 20.4%).

Compound **3**, syrup, had $[\alpha]_D$ −39° (*c* 1), R_F 0.40 (solvent *D*).

Compound **5** had m.p. 174–175° (from ethyl acetate–hexane), $[\alpha]_D$ −121.2° (*c* 1), R_F 0.32 (solvent *D*).

Anal. Calc. for $C_{34}H_{34}O_6$: C, 75.82; H, 6.36. Found: C, 75.74; H, 6.35.

The n.m.r. data are listed in Tables I and II.

Methyl 2-O-acetyl-3-O-benzyl-4-O-(2,3,4-tri-O-acetyl-β- and -α-D-xylopyranosyl)-β-D-xylopyranoside (**7** *and* **8**). — Glycosylation of **3** (295.9 mg, 0.55 mmol) with **6**[1,2] (142.5 mg, 0.5 mmol) was performed in dichloromethane (2 mL) for 17 h at room temperature in the presence of triphenylmethylium perchlorate (17 mg, 0.05 mmol), using a vacuum technique[1]. Column chromatography (solvent *F*) of the product gave **7** (235 mg, 84%) and **8** (8 mg, 3%).

Compound **7** had m.p. 139–140° (from ethyl acetate–hexane), $[\alpha]_D$ −67° (*c* 1), R_F 0.26 (solvent *B*).

Anal. Calc. for $C_{26}H_{34}O_{13}$: C, 56.31; H, 6.18. Found: C, 56.33; H, 6.22.

Compound **8**, syrup, had $[\alpha]_D$ +32.5° (*c* 0.8), R_F 0.28 (solvent *B*).

The n.m.r. data for **7** and **8** are listed in Tables I and II.

Competitive glycosylation of the trityl ethers **1** *and* **3**. — Glycosylation of a mixture of **1** (269.5 mg, 0.55 mmol) and **3** (295.9 mg, 0.55 mmol) with **6** (142.5 mg, 0.50 mmol) in the presence of triphenylmethylium perchlorate (17 mg, 0.05 mmol) in dichloromethane (3 mL) was performed under the conditions for the synthesis of **7** and **8**. The mixture of products contained (t.l.c.) **1** and **7** [major products, R_F 0.85 and 0.26, respectively (solvent *B*)], **3**, **8**, **9**, and **10** [minor products, R_F 0.92, 0.28, 0.19, and 0.22, respectively (solvent *B*)]. Column chromatography (solvent *F*) of the mixture gave **1** (190 mg, 70%) and **7** (210 mg, 76%), which were identified by n.m.r. spectroscopy.

Glycosylation of the trityl ether **2**. — The reaction of **6** (142.5 mg, 0.5 mmol) with **2** (322 mg, 0.55 mmol) in dichloromethane (2 mL) in the presence of triphenylmethylium perchlorate (17 mg, 0.05 mmol) was performed as described for the synthesis of **7** and **8**. Column chromatography (solvent *F*) gave the product **11** [155

mg, 51%, R_F 0.20 (ethyl acetate–benzene, 7:33)] and a mixture (15 mg) of **11** and its α-(1→4)-linked isomer.

Catalytic hydrogenolysis of **11** (10% Pd/C, EtOH, 40°, 2 h) followed by deacetylation with methanolic sodium methoxide gave a quantitative yield of a mixture of methyl xylobiosides **12** and **13**, the ^{13}C-n.m.r. spectra data of which are listed in Table III.

*Methyl 2,3,4-tri-*O*-benzyl-β-*D*-xylopyranoside* (**14**). — Methyl β-D-xylopyranoside (330 mg, 2 mmol) was treated with benzyl chloride (1.5 mL, 13 mmol) and sodium hydride (600 mg of an 80% dispersion in mineral oil, 20 mmol) in *N,N*-dimethylformamide (20 mL), followed by conventional work-up and column chromatography (solvent *E*), to give **14** (860 mg, quantitatively yield), m.p. ~30°, $[\alpha]_D$ +8° (*c* 1), R_F 0.52 (solvent *D*) and 0.26 (solvent *C*).

The n.m.r. data for **14** are listed in Tables I and II.

Anomerisation of **14**. — Treatment of **14** (217 mg, 0.5 mmol) with triphenylmethylium perchlorate (17 mg, 0.05 mmol) in dichloromethane (2 mL) for 17 h and column chromatography (solvent *E*) gave **15** (133 mg, 61.3%), $[\alpha]_D$ +22° (*c* 1), R_F 0.21–0.26 (solvent *C*).

The ^{13}C-n.m.r. data for **15** are listed in Table II.

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