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Note

Glycosylation by 1,2-*O*-cyanoethylidene derivatives of carbohydrates

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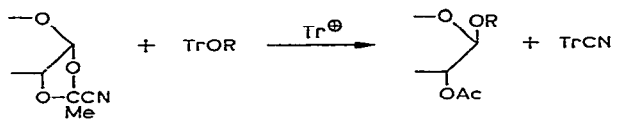
A new approach to the synthesis of 1,2-*trans*-glycosides has been recently suggested[1]. It involves the reaction of a 1,2-*O*-cyanoethylidene sugar derivative **1** with a trityl ether **2** in the presence of a triphenylmethylium salt as catalyst:

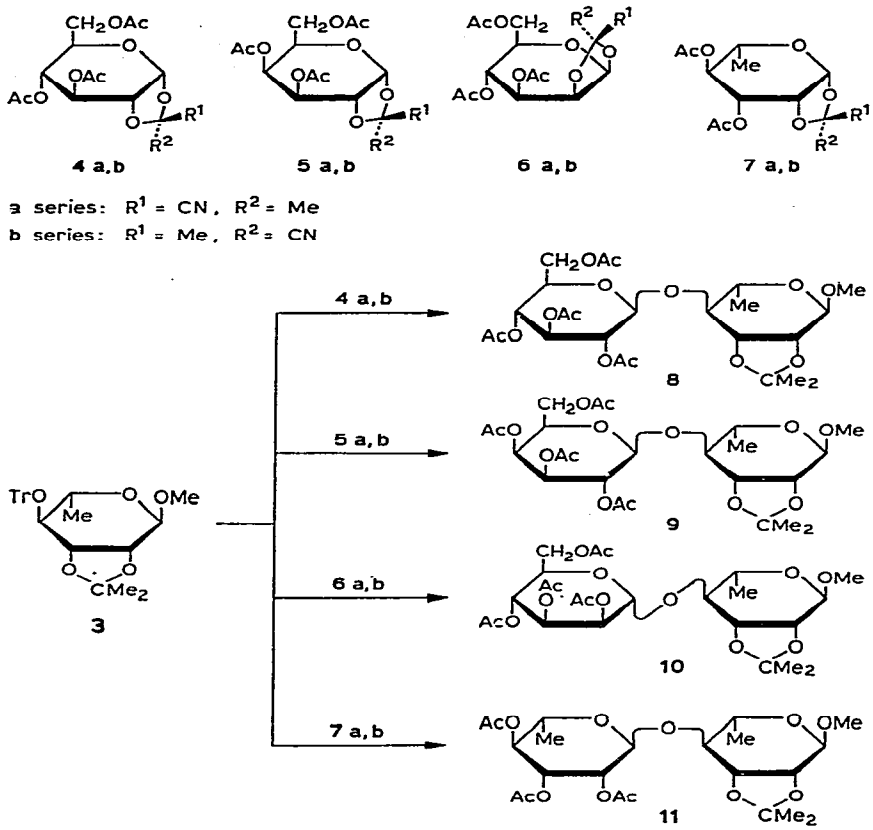


1 2

This reaction has been applied to the synthesis of several disaccharides[1,2] and polysaccharides[3,4], glycosylation being carried out by derivatives **1** possessing the D-*gluco* configuration. A recently developed, general procedure[5] enables the efficient synthesis of such compounds belonging to the D-*galacto*-, D- and L-*manno*-, and D-*gluco* series.

In order to elucidate the general character of this type of glycosylation and, especially, its stereospecificity, we have studied the reaction of methyl 2,3-*O*-isopropylidene-4-*O*-trityl-α-L-rhamnopyranoside (**3**) with each of the following diastereomeric ketals: 3,4,6-tri-*O*-acetyl-1,2-*O*-[1-(*exo*- and *endo*-cyano)ethylidene]-α-D-glucopyranose (**4a,b**), 3,4,6-tri-*O*-acetyl-1,2-*O*-[1-(*exo* and *endo*-cyano)ethylidene]-α-D-galactopyranose (**5a,b**), 3,4,6-tri-*O*-acetyl-1,2-*O*-[1-(*exo*- and *endo*-cyano)ethylidene]-β-D-mannopyranose (**6a,b**), and 3,4-di-*O*-acetyl-1,2-*O*-[1-(*exo*- and *endo*-cyano)ethylidene]-β-L-rhamnopyranose (**7a,b**). The formation of the known[6–9] disaccharide derivatives **8–11** was expected.

Condensation of the cyanoethylidene derivatives **4–7** with **3** was performed in dichloromethane in the presence of 0.10 equivalent of triphenylmethylium perchlorate[10] at room temperature using a vacuum technique. The yields and properties of compounds **8–11** isolated by column chromatography on silica gel are listed in Table I. As can be seen from Table I, the yields of the products of glycosylation do not depend significantly on the nature of the sugar derivative used (thus indicating



the method's general character) or on the stereochemistry at C-2 of the dioxolane ring in the cyanoethylidene derivatives. In fact, glycosylation of **3** by a mixture of diastereomeric ketals (**5a** + **5b**) that is directly obtainable from the reaction of acetobromogalactose with potassium cyanide[5] afforded **9** in 92% yield. It is noteworthy that, in this case, the glycosylation was performed without recourse to the vacuum technique. Under analogous conditions, the reaction of **3** with **6a** gave **10** in 88% yield.

The properties of the disaccharide derivatives obtained were in close agreement with those reported, thus demonstrating the high stereospecificity of this glycosylation reaction. The degree of stereospecificity was established for the synthesis of **10**. The ratio of the isomeric mannopyranosyl-rhamnoses (differing in configuration at the mannosyl bond) present in the mother liquor after recrystallization of **10** was determined by means of anion-exchange chromatography (with authentic 4-*O*-α-D-mannopyranosyl-L-rhamnose[8] and 4-*O*-β-D-mannopyranosyl-L-rhamnose[11] as standards), and the total content of the disaccharide derivative **10** accounted for more than 99% of the glycosylation product.

The data reported here demonstrate that 1,2-*O*-cyanoethylidene derivatives of

TABLE I

YIELDS AND PROPERTIES OF THE GLYCOSYLATION PRODUCTS **8–11**

Glycosylating agent	*Product*	*Yield (%)*	*M.p. (degrees)*	$[\alpha]_D$ *(degrees) (c, chloroform)*	*Lit. data*		
					m.p. (degrees)	$[\alpha]_D$ *(degrees)*	*Ref.*
4a		97	156–157	−28.5 (1.53)			
	8				158–159	−30.6	6
4b		92	155–156.5	−29.0 (1.76)			
5a		100	189–191	−22.7 (1.71)			
	9				192–193	−24.4	7
5b		88	189–190.5	−21.2 (1.59)			
6a		99	117–118	+28.7 (1.51)			
	10				119–120	+30.7	8
6b		84	116–118	+29.1 (1.88)			
7a		94	syrup	−70.5 (1.37)			
	11				syrup	−74.0	9
7b		94	syrup	−69.0 (1.81)			

carbohydrates are effective glycosylating reagents for the stereospecific synthesis of 1,2-*trans*-glycosides in high yields.

EXPERIMENTAL

Nitromethane was distilled from urea at 100 mmHg and then from CaH_2. Dichloromethane was washed with conc. H_2SO_4 and water, dried with $CaCl_2$, and distilled from CaH_2. 1,2-*O*-Cyanoethylidene derivatives **4–7** were obtained as described elsewhere[5]. Column chromatography was performed on silica gel L (100–250 μm, CSSR) with a gradient of benzene→ethyl acetate. T.l.c. was performed on silica gel LS (5–40 μm, CSSR) with 2:3 benzene–ethyl acetate. Anion-exchange chromatography was performed on a 71 100A (CSSR) instrument with a glass column (30 × 0.6 cm) packed with DA X4 (Durrum, U.S.A.) resin, a 0.7M sodium borate buffer (pH 7.7) at 55°, and an elution rate of 20 ml/h. The p.m.r. spectrum ($CDCl_3$, internal Me_4Si) was recorded with a Tesla BS-497 100-MHz (CSSR) instrument. Optical rotations of chloroform solutions were measured with a Perkin–Elmer 141 polarimeter at 20 ±2°, and melting points with a Kofler apparatus. Solutions were concentrated *in vacuo* at 40°.

Methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside. — Methyl α-L-rhamno-

pyranoside [m.p. 104–105° (ethyl acetate), $[\alpha]_D$ −61.5° (*c* 1.5, water)][12] (14.0 g) and anhydrous copper sulfate (200 g) were shaken with dry acetone (700 ml) for 10 h at room temperature. The mixture was filtered, the residue was washed with chloroform, and the combined solutions were taken to dryness to yield the title compound (17.0 g, 99%) as a colourless, chromatographically homogeneous, thick syrup, $[\alpha]_D$ −19° (*c* 7.0); lit.[6] $[\alpha]_D$ −16.4° (*c* 3.1, acetone).

Methyl 2,3-O-isopropylidene-4-O-triphenylmethyl-α-L-rhamnopyranoside (**3**). — To a solution of the foregoing compound (3.6 g, 16.5 mmol) and 2,4,6-collidine (2.0 g, 16.5 mmol) in dichloromethane (50 ml) was added triphenylmethylium perchlorate[10] (5.2 g, 15.0 mmol) during 10–15 min with stirring. After 1 h, the decolorized reaction mixture was diluted with chloroform (50 ml) and washed with water (3 × 50 ml). The organic layer was concentrated, and the residue was subjected to column chromatography in benzene to yield the chromatographically homogeneous product (4.8 g). This was crystallized from methanol (30 ml) at −5° to give **3** (3.5 g, 51%), m.p. 83–84°, $[\alpha]_D$ −75° (*c* 2.2); lit.[2] syrup, $[\alpha]_D$ −68.5° (chloroform). P.m.r. data: δ 7.40–7.10 (15 H, aromatic), 4.49 (s, 1 H, H-1), 4.09–3.62 (4 H, H-2,3,4,5), 3.30 (s, 3 H, OCH_3), 1.13 and 1.02 (2 s, 6 H, isopropylidene), and 0.89 (d, 3 H, *J* 6.4 Hz, C-CH_3).

Anal. Calc. for $C_{29}H_{32}O_5$: C, 75.62; H, 7.00. Found: C, 75.92; H, 7.23.

Syntheses of disaccharide derivatives **8–11**. — In one limb of a tuning fork-shaped tube ($\overset{|}{\cap}$) was placed a solution of **3** (0.54 mmol) and each of the ketals **4–7** (0.50 mmol) in nitromethane (1.5 ml), and in the other limb, a solution of triphenylmethylium perchlorate (0.05 mmol) in nitromethane (0.2 ml), and the solutions were freeze-dried. Nitromethane (1.0 ml) was distilled (10^{-3} mmHg) from CaH_2 into the first limb, and lyophilisation was repeated followed by drying of the residues for several h. Dichloromethane (3.0 ml) was distilled (10^{-3} mmHg) from CaH_2 into the tube, and the solutions were mixed and left at room temperature for 15 h. The bright-yellow reaction mixture was treated with 1:1 methanol–pyridine (0.5 ml), and the decolorized solution was diluted with chloroform (50 ml) and washed with water (2 × 30 ml). The organic layer was evaporated and the residue was subjected to column chromatography. Appropriate fractions were combined and taken to dryness, and ethanol was distilled from the residue *in vacuo*. The yields and properties of the disaccharide derivatives **8–11** thus obtained are listed in Table I.

Methyl 2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-α-L-rhamnopyranoside (**9**). — A solution of **3** (1.20 g, 2.6 mmol) and a mixture of ketals **5a** + **5b** (3:1, see Ref. 5; 0.89 g, 2.49 mmol) in dichloromethane (30 ml) was evaporated to dryness, and fresh solvent (30 ml) was distilled from the residue which was then dissolved in dichloromethane (10 ml) and treated with triphenylmethylium perchlorate (86 mg, 0.25 mmol) for 18 h at room temperature. Methanol–pyridine (1:1, 1 ml) was added to the mixture, and the colourless solution was diluted with 1:2 chloroform–hexane (100 ml) and washed with water (2 × 50 ml). The upper, organic layer was evaporated, and the residue was subjected to column chromato-

graphy to yield crystalline **9** (1.30 g). Recrystallization from ethanol (2 ml) afforded 1.25 g (91.5%) of **9**, m.p. 188–190°, $[\alpha]_D$ −22° (*c* 2.5).

Methyl 2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-α-L-rhamnopyranoside (**10**). — Triphenylmethylium perchlorate (86 mg, 0.25 mmol) was added to a solution of **3** (1.20 g, 2.6 mmol) and **6a** (0.89 g, 2.49 mmol) in dichloromethane (10 ml). After 6 h, the mixture was worked-up as described above. Column chromatography and recrystallization of the crystalline product (1.30 g) from ethanol (2 ml) afforded 1.20 g (87.9%) of **10**, m.p. 117–118°, $[\alpha]_D$ +30° (*c* 3.2).

The mother liquor from the recrystallization of **10** was evaporated to dryness, and the residue (100 mg) was dissolved in chloroform (10 ml), and trifluoroacetic acid (2 ml) containing 1% of water was added. After 1 h at room temperature, the mixture was taken to dryness, toluene (3 × 50 ml) was distilled from the residue *in vacuo*, and the residue was then dissolved in acetic anhydride (2 ml) and treated with 1% (v/v) conc. H_2SO_4 in acetic anhydride (4 ml) at room temperature for 2 h. The mixture was poured into ice–water (100 ml), left for 12 h, and extracted with chloroform (3 × 30 ml), and the organic layer was washed with saturated, aqueous sodium hydrogen carbonate (2 × 30 ml) and evaporated. A solution of the residue in 10% (v/v) triethylamine in methanol (5 ml) was kept at room temperature for 20 h and then taken to dryness, the residue was dissolved in water, and an aliquot of the solution was subjected to anion-exchange chromatography. 4-*O*-α-D-Mannopyranosyl-L-rhamnose (*t* 77 min) and 4-*O*-β-D-mannopyranosyl-L-rhamnose (*t* 52 min) were detected (in comparison with authentic samples) in the ratio 8:1.

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