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Note

Preparation of ether-linked disaccharides having D-xylose coupled to other monosaccharides

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Naturally occurring disaccharides involving *O*-glycosidic linkages are common[1–4], whereas relatively few nonglycosidically *O*-linked disaccharides are known[5–7]. For example, Prystas[5] obtained disaccharides of the type D-ribose-(5 → 4)-D-glucose, by reacting a D-ribose derivative having HO-5 unprotected with a 2-*O*-alkyl-1,6 : 3,4-dianhydro-D-galactopyranose using either $BF_3 \cdot Et_2O$ in benzene–ether or NaH in Me_2SO. The latter conditions to gave better yields and hence such methodology was adopted here to effect ring opening of the anhydro moiety of sugar derivatives and give ether-linked disaccharides.

As a part of a programme aimed at the synthesis of novel derivatives of D-xylose, initial attention was directed towards the preparation of a series of functionalized disaccharides having the general structures D-xylose-(5 → *n*)-Su and D-xylose-(3 → *n*)-Su, where D-xylose is attached by an ether linkage to a sugar (Su) comprising D-glucose, D-fructose, D-mannose, or xylitol: all sugars were in the form of acetal derivatives. A nonglycosidic junction was deliberately chosen in order to effect improved stability to hydrolysis over disaccharides involving attachment by glycosidic linkages.

Derivatives of the type D-*xylose-(5 → n)-Su.*—We report herein the synthesis of the nonglycosidically linked disaccharides **2a–d**, which were obtained by condensation of the sugar unit SuOH with 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose[8] (**1**) (Scheme 1).

The SuOH unit used in each condensation was in the form of a diacetal derivative (identified as Ip_2Glc-3-OH, Ip_2Fru-1-OH, Ip_2Fru-3-OH, and Ip_2Xyl-5-OH, respectively, in Scheme 1)[9] in order to facilitate the regioselective functional-

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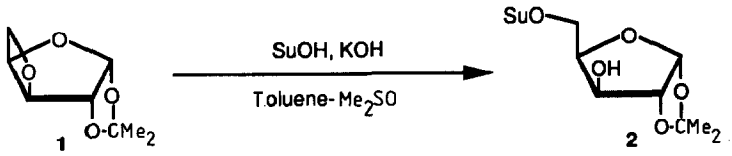
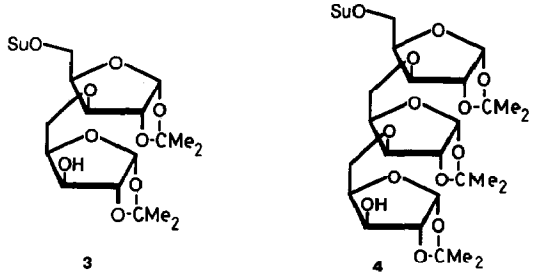


2a Su = 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl (SuOH = Ip_2Glc-3-OH)
2b Su = 1-deoxy- 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranos-1-yl (SuOH = Ip_2 Fru-1-OH)
2c Su = 3-deoxy-1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose-3-yl (SuOH = Ip_2Fru-3-OH)
2d Su = 5-deoxy-1,2:3,4-di-*O*-isopropylidene-DL-xylit-5-yl (SuOH = Ip_2Xyl-5-OH)

Scheme 1.

ization of the product obtained following the controlled deprotection of the acetal groups. It should be noted that the basic conditions of the reaction media allowed the concomitant formation of trisaccharides **3a–d** and tetrasaccharides **4a–d**, by sequential attack respectively of the products **2a–d** and **3a–d**, in their alkoxide ion forms, on the anhydro derivative **1**.



The majority of these reactions were effected using the reagents SuOH, KOH, and **1** in the proportion 2:4:1 and the solvent mixture 1:1 toluene–Me_2SO at 80°C. Table I shows the relative percentages of the products **2a–d**, **3a–d**, and **4a–d** obtained as determined by HPLC and the yields of products **2a–d** isolated after a reaction time of 120 h.

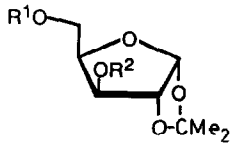
The results showed (Table I) that: a decrease in the concentration of Me_2SO in the solvent mixture, decreases the rate of the reaction (120 h with 50% Me_2SO; 216 h with 20% Me_2SO) but did not affect the distribution of the products (reactions 1 and 2); under the same reaction conditions, the distribution of the products was unaffected by the nature of SuOH; the distribution of the products was subject to the initial proportions used of SuOH, KOH, and **1**. When the proportions of SuOH, KOH and **1** were changed from 2:4:1 to 1:2:1 (reactions 1 and 3, respectively, Table I), products of the type **2a–d** were still the major components, whereas the proportion of corresponding trimer **3** increased from 18 to 32%.

TABLE I

Distribution of the products formed with 2:4:1 SuOH–KOH–**1**; solvent, 1:1 toluene–Me_2SO at 80°C, after 120 h

Expt no.	SuOH	Junction $5 \rightarrow n$	**1** Remaining (%)	Distribution [a] **2:3:4**	Yield of **2** (%)
1	Ip_2Glc-3-OH	5 3	10	76:18:6	46
2 [b]	Ip_2Glc-3-OH	5 3	12	75:18:7	45
3 [c]	Ip_2Glc-3-OH	5 3	5	61:32:7	38
4	Ip_2Fru-1-OH	5 1	4	78:20:2	50
5	Ip_2Fru-3-OH	5 3	11	77:20:3	44
6	Ip_2Xyl-5-OH	5 5	4	75:21:4	51

[a] Ratios were determined by direct comparison of peak areas as determined using a differential refractometer detector and were not corrected by direct comparison with isolated products. [b] 4:1 toluene–Me_2SO after 216 h. [c] 1:2:1 SuOH–KOH–**1**.



5a $R^1 = H$ $R^2 = H$
5b R^1 = 3-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-3-yl
R^2 = 5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl
5c $R^1 = H$ $R^2 = C_8H_{17}$
5d $R^1 = C_8H_{17}$ $R^2 = H$
5e R^1 = All $R^2 = H$

The site of substitution of the D-xylose moiety of compounds of the type D-xylose-(5 → *n*)-Su was determined by comparison of ^{13}C NMR data obtained for a variety of disaccharides and *O*-alkyl derivatives of 1,2-*O*-isopropylidene-α-D-xylofuranose[10,11] (Table II). The signals for C-1 and C-4 of the D-xylose moiety and of 1,2-*O*-isopropylidene-α-D-xylofuranose (**5a**) were found to be similar for the range of compounds selected for the study and, therefore, not of diagnostic value. However, differences were observed for signals assigned to C-2, C-3, and in particular C-5. Either an alkyl or sugar substituent attached by an ether linkage at C-3 resulted in a shielding effect on C-2 (2.2–3.4 ppm) and deshielding effect on C-3 (0.5–5.5 ppm): such evidence is supportive of the structures **2a–d** in which the HO-3 group is unsubstituted. The signal assigned to C-5 of the xylose moiety showed significant differences between 5-O substituted derivatives. Thus, an O-5 ether linkage is associated with a large deshielding effect on C-5 (7.9–13.1 ppm). These data further support the structures identified for compounds of the type D-xylose-(5 → *n*)-Su (Scheme 1). For each of the compounds studied (**2a–d**), the signal for the carbon of moiety Su involved in *O*-ether linking was shifted downfield of the corresponding substrates SuOH (Scheme 1, Table II) possessing free hydroxyl groups.

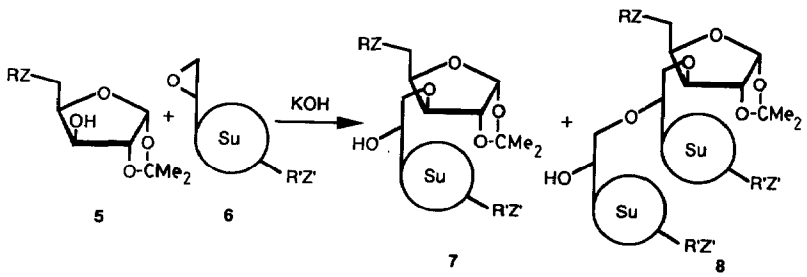
Such structural assignments are in accordance with the expected attack of a nucleophile on the least sterically hindered carbon of the anhydro derivative **1**.

The experimental conditions identified in Table I were optimum for the preferential preparation of the disaccharide derivatives of type **2** (Table III). To

improve the yield of corresponding trisaccharide derivatives of type **3**, it was found necessary to perform a separate reaction involving, the anhydro derivative **1** with a disaccharide substrate of type **2**. The latter approach might also permit the preferental synthesis of trisaccharides of the type Su-($n \rightarrow 3$)-D-xylose-(5 $\rightarrow n$)-Su: thus a disaccharide of type **2** could be condensed with an anhydro derivative of a third monosaccharide unit Su.

Derivatives of the type D-*xylose-(3* $\rightarrow$ n*)-Su.*—We have synthesized compounds of the type D-xylose-(3 $\rightarrow n$)-Su using the strategy outlined in Scheme 2. These syntheses were effected using the same conditions used for compounds of the type the D-xylose-(5 $\rightarrow n$)-Su (Expt 1, Table I), but with SuOH substituted with 5-*O*-allyl-1,2-*O*-isopropylidene-α-D-xylofuranose[9] (**5e**, RZ = CH_2=CH–CH_2O) and the anhydro derivative **1** with *n*-dodecyl-5,6-anhydro-2,3-*O*-isopropylidene-α-D-mannofuranoside[9] (**6e**, Su = 2,3-*O*-isopropylidene-α-D-mannofuranoside, R′Z′ = *n*-$C_{12}H_{25}O$). After purification by column chromatography, the *n*-dodecyl 6-*O*-(5-*O*-allyl-3-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-3-yl)-2,3-*O*-isopropylidene-α-D-mannofuranoside derivative (**7e**, RZ = CH_2=CH–CH_2O, R′Z′ = *n*-$C_{12}H_{25}O$) was isolated in 74% yield, together with the trisaccharide derivative (**8e**, RZ = CH_2=CH–CH_2O, R′Z′ = *n*-$C_{12}H_{25}O$) in 8% yield (Table III). It should be mentioned that, during analysis of the relative composition of the products by HPLC (prior to the purification of the mixture), no trace of a tetrasaccharide derivative was found. The yield of the trisaccharide derivative **8** could be increased by reacting pure compound **7** directly with the anhydro substrate **6**.

The site of substitution on the D-mannose moiety of compounds of the type D-xylose-(3 $\rightarrow n$)-Su was deduced following a comparative study of ^{13}C NMR data (Table II). Thus whilst little difference was observed for the signals for C-1 to C-5 between the disaccharide **7e** and *n*-dodecyl 2,3-*O*-isopropylideneα-D-mannofuranoside, a marked deshielding effect (8.3 ppm) was observed resulting from the ether linkage at C-6 of **7e**. Such an observation is in agreement with the expected preferred attack at the least hindered carbon of the anhydro moiety of **6**.



Scheme 2.

EXPERIMENTAL

General methods.—Melting points were determined on an electrothermal automatic apparatus, and are uncorrected. Optical rotations for solutions in $CHCl_3$ were measured with a digital polarimeter DIP-370 (Jasco) at 25°C. NMR spectra were recorded with a Bruker WP-300 instrument for solutions in $CDCl_3$ (internal Me_4Si). Elemental analyses were performed by the Service Central de Micro-Analyse du Centre National de la Recherche Scientifique (Vernaison, France). Reactions were monitored by either HPLC (Waters 721), using either of the reverse phase columns RP-18 (Merck) or PN 27-196 (Waters) or CPG (Girdel) with columns of either OV 17 or SE 30. Column chromatography was performed on Silica Gel (60 mesh, Matrex) by gradient elution with hexane–acetone (in each case the ratio of silica gel to product mixture to be purified was 30:1). For physicochemical and elemental analyses see Table II and Table III. Diacetal derivatives (SuOH), namely, 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (Ip_2Glc-3-OH), 2,3 : 4,5-di-*O*-isopropylidene-β-D-fructopyranose (Ip_2Fru-1-OH), 1,2 : 4,5-di-*O*-isopropylidene-β-D-fructopyranose (Ip_2Fru-3-OH), 1,2 : 3,4-di-*O*-isopropylidene-DL-xylitol, were synthesized in accordance with the method of Regnaut[9].

General procedure for the preparation of 5-O-(n-deoxy-Su-n-yl)-1,2-O-isopropylidene-α-D-xylofuranose (**2**) *(n = 1, 3, or 5).*—Finely powdered KOH (4 equiv) and the anhydro derivative **1** (1 equiv) were added to a stirred solution of the appropriate SuOH (2 equiv) in 1:1 toluene–Me_2SO (100 g.L^{-1}). After 120 h at 80°C, the mixture was filtered and the filtrate neutralized with satd aq NH_4Cl. The organic phase was separated, washed with water (twice), dried (Na_2SO_4), and evaporated under diminished pressure. The desired products **2a–d** were isolated after purification by column chromatography.

5-O-(3-Deoxy-1,2 : 5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl)-1,2-O-isopropylidene-α-D-xylofuranose (**2a**).—The foregoing procedure applied to Ip_2Glc-3-OH (15.1 g, 58 mmol) gave, after chromatography on a column of silica gel using 19:1 hexane–acetone, a fraction which was a mixture of **3a** and **4a** (1.9 g). Further elution with 93:7 hexane–acetone gave **2a** (6 g, 46%). To permit characterisation of **3a**, a sample was obtained by further chromatography on a column of silica gel of the foregoing fraction of the mixture of **3a** and **4a**.

5-O-(1-Deoxy-2,3 : 4,5-di-O-isopropylidene-β-D-fructopyranos-1-yl)-1,2-O-isopropylidene-α-D-xylofuranose (**2b**).—Likewise Ip_2Fru-1-OH (7.5 g, 29 mmol) gave, after column chromatography on silica gel using 19:1 hexane–acetone, a fraction which was a mixture of **3b** and **4b** (0.7 g). Further elution with 93:7 hexane–acetone gave **2b** (2.5 g, 50%).

5-O-(3-Deoxy-1,2 : 4,5-di-O-isopropylidene-β-D-fructopyranos-3-yl)-1,2-O-isopropylidene-α-D-xylofuranose (**2c**).—Likewise Ip_2Fru-3-OH (9 6, 34.8 mmol) gave, after column chromatography on silica gel using 24:1 hexane–acetone, a fraction that was a mixture of **3c** and **4c** (0.6 g). Further elution with 93:7 hexane–acetone

TABLE II

^{13}C NMR [a] spectral data (δ values) for compounds **2a–d**, **7e** and derivatives of 1,2-*O*-isopropylidene-α-D-xylofuranose (**5a–e**) measured at 75 MHz in chloroform-*d*

C	5a	5b	5c	5d	5e	2a			2b			2c			2d			7e [d]		
						X [b]	Su [c]	SuOH	X	Su	SuOH	X	Su	SuOH	X	Su	SuOH	X	Su	SuOH
C-1	104.6	105.1	103.8	104.8	103.8	104.7	105.1	105.1	104.7	73.8	65.3	104.3	72.1	72.2	104.8	65.5	65.8	105.0	106.0	105.8
C-2	85.2	82.9	82.1	85.4	84.3	85.5	82.2	85.0	85.0	102.2	102.9	84.7	101.9	104.4	85.2	76.3	75.3	78.2	84.7	84.6
C-3	74.9	81.7	81.4	75.6	75.1	75.9	83.3	74.8	75.4	70.7	70.8	74.1	78.3	70.7	75.7	77.9	77.3	83.6	78.9	79.9
C-4	80.2	79.3	79.5	77.8	77.2	77.9	81.0	81.1	78.1	69.9	69.9	78.8	75.5	77.1	78.5	83.4	78.3	79.7	82.3	79.1
C-5	59.9	67.8	59.4	69.1	71.8	68.3	72.3	73.0	69.6	70.2	70.7	69.1	72.1	73.2	68.3	71.7	62.3	72.5	69.0	69.9
C-6							67.5	67.5		60.9	61.1		60.2	60.7					72.6	64.3

[a] Additional signals present in all spectra were, 108.5–112.4 $\underline{C}Me_2$ and 23.9–26.7 $C\underline{Me}_2$. [b] X: Xylosyl moiety in each of the disaccharides **2a–d** and **7e**. [c] Su: Glycosyl moiety in each of the disaccharides **2a–d** and **7e**. [d] SuOH: *n*-dodecyl 2,3-O-isopropylidene-α-D-mannofuranoside.

TABLE III

Physicochemical and microanalytical data for disaccharides and trisaccharides

Compound	Mp (°C)	$[\alpha]_D^{25}$ $CHCl_3$	Formula	Calcd		Found	
				C	H	C	H
2a	113–115	−31.1° (*c* 1.7)	$C_{20}H_{32}O_{10}$	55.54	7.46	55.65	7.43
2b	oil	−20.5° (*c* 1.1)	$C_{20}H_{32}O_{10}$	55.54	7.46	54.95	7.73
2c	120–122	−85.6° (*c* 1.6)	$C_{20}H_{32}O_{10}$	55.54	7.46	55.72	7.52
2d	oil	−7.5° (*c* 1.4)	$C_{19}H_{26}O_9$	57.28	6.58	57.20	6.52
3a	oil	−45.1° (*c* 0.6)	$C_{28}H_{44}O_{14}$	55.62	7.33	55.78	7.48
7e	oil	−7.0° (*c* 1.1)	$C_{32}H_{56}O_{10}$	63.97	9.39	64.15	9.28
8e	oil	−22.2° (*c* 0.1)	$C_{53}H_{93}O_{15}$	65.60	9.66	65.48	9.55

gave **2c** (2.1 6, 44%).

*5-O-(5-Deoxy-1,2 : 3,4-di-O-isopropylidene-*DL*-xylit-5-yl)-1,2-O-isopropylidene-α-*D*-xylofuranose* (**2d**).—Likewise 1,2 : 3,4-di-*O*-isopropylidene-DL-xylitol (3.9 g, 16.8 mmol) gave, after column chromatography on silica gel using 19 : 1 hexane–acetone, a fraction that was a mixture of **3d** and **4d** (0.5 g). Further elution with 47 : 3 hexane–acetone gave **2d** (1.7 g, 51%).

n-*Dodecyl 6-O-(5-O-allyl-3-deoxy-1,2-O-isopropylidene-α-*D*-xylofuranos-3-yl)-2,3-O-isopropylidene-α-*D*-mannofuranoside* (**7e**).—The foregoing procedure applied to compound **6e**[10] (2.3 g, 6.1 mmol) gave, after column chromatography on silica gel using 9 : 1 hexane–acetone, **8e** (0.3 g). Further elution with 17 : 3 hexane–acetone gave **7e** (2.8 g, 74%).

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