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Synthesis of Ether-linked Disaccharide and Trisaccharide Derivatives of the Type (3-5)-D-Xylan

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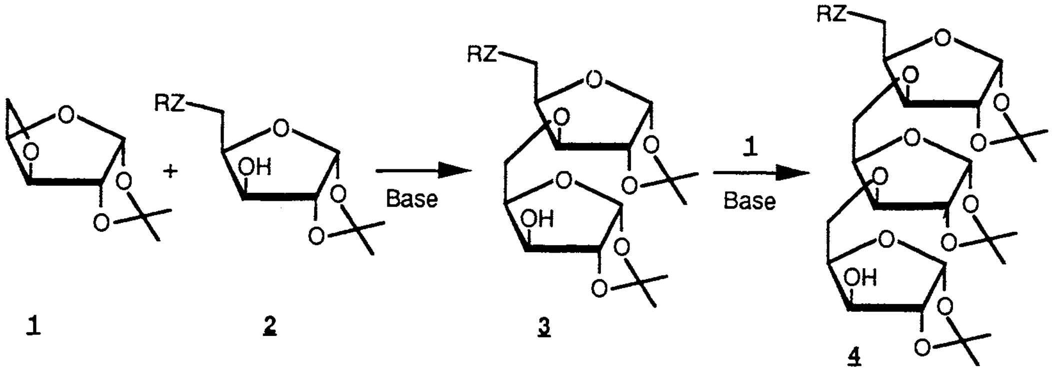
We have synthesized a series of non-glycosidically linked di- and trisaccharide monoethers of the type (3-5)-D-xylan, by a one-pot reaction between the alcohol ROH and 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose, in the presence of KOH and toluene-DMSO at 80 °C.

The naturally occurring xylans, which are the major constituant of hemicelluloses,[1)] are polysaccharides formed of repeated D-xylose units attached by (1-4)-glycosidic linkages.[2)] Myrhe and Smith [3)] have successfully achieved the synthesis of such D-xylans. Alternatively, Uryu *et al.* [4-6)] have prepared series of xylans with either (1-5)- or (3-5)- attachments by the polymerization of either 1,5-anhydro-2,3-di-*O*-benzyl-β-D-xylofuranose or 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose respectively. Each of these polymerisations gave both stereoregular and nonstereoregular substituted xylans. After deprotection, a stereoregular (3-5)-D-xylofuranan was obtained by starting from the latter monomer.

We now report the synthesis of related oligomers in which the monomeric units are attached, solely, by ether linkages. Thus derivatives of disaccharide 3 and trisaccharide 4 were synthesized which have D-xylose-(3-5)-D-xylose linkages possessing one functional group free for a second regiospecific derivatisation to be effected. The route to such compounds (Scheme 1), involves condensation of 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose (1) [7)] with monoacetal derivatives of the type 5-R-Z-1,2-*O*-isopropylidene-α-D-xylofuranose (2) in the presence of a base. The latter compound which reacts as the alkoxide ion and possesses a C-5-R-Z functionalized group (where for e.g. Z= O, S or NH) is resistant to the basic conditions of this reaction. In this reaction, we also have the concomitant formation of a trisaccharide derivative 4, obtained by condensation of product 3 (in the alkoxide form) on the anhydro derivative 1. The potential to introduce a second functional group on the products 3 and 4 may be facilitated by substitution at the C-3 free hydroxyl group.

The work described herein concerned the synthesis of compounds 3 and 4 in which the alkyl chain R-Z, was an ether in which Z= O. These compounds were obtained in a one-pot reaction, by allowing different alcohols (ROH) to condense with the anhydro derivative 1, in the presence of finely powdered KOH in toluene-DMSO at 80 °C. Under these conditions the derivative 2 is formed *in situ* by attack of the alkoxide ion RO$^-$ on the anhydro derivative 1. Also the product 2 formed (in the alkoxide form) can condense concomitantly with



Scheme 1.

the derivative 1 to give the (3-5)-disaccharide 3. The alkoxide form of the produced disaccharide 3 once more, can attack the anhydro derivative 1 to form the (3-5)-trisaccharide 4.

We have studied the influence of various reaction parameters (relative proportions of reactants, nature of ROH, composition of solvent and temperature) which favours the formation of disaccharide derivative 3 over that of the competing products 2 and 4. All reactions were performed with an excess of KOH (2 eq. for 1 eq. of ROH) to enhance the formation of the alkoxide ion. The results presented in Table 1 indicate the relative percentages of the products 2, 3 and 4 (measured by HPLC) and yields of the isolated products 3.[8)]

Table 1. Distribution of the products following the addition of an alcohol (ROH) on the anhydro derivative 1 (1 eq.) after 90% completion of the reaction obtained using toluene-DMSO [4:1, (v/v)] at 80 °C

R-OH	exp. n°	eq. ROH	eq. KOH	t / h	Distribution / % [a)] 2 - 3 - 4	Yield / % 3
CH_2=CH-CH_2- (a)	1	1.2	2.4	20	24 : 70 : 6	37
	2 [b)]	1.2	2.4	10	20 : 72 : 8	41
	3 [c)]	1.2	2.4	40	22 : 71 : 7	-
	4	3	6	17	65 : 34 : 1	21
PhCH_2- (b)	5	1.2	2.4	19	30 : 63 : 7	36
	6	3	6	36	78 : 22 : -	14
$C_{12}H_{25}$- (c)	7	1.2	2.4	19	31 : 66 : 3	35
$C_{16}H_{33}$- (d)	8	1.2	2.4	21	30 : 67 : 3	34

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) Toluene-DMSO [1:1, (v/v)]. c) 60 °C.

Upon examination of Table 1 it appears that: The anhydro derivative 1 must form degradation products (which are not detected) as the yield of the isolated disaccharide product 3 is lower than that expected from the HPLC measurement of the relative proportions of 2, 3 and 4 (before purification).

The distribution of the products 2, 3 and 4 seems to be unaffected by the composition of the solvent and the reduction of the temperature, as shown in the results of reactions 1 and 2 (in which the composition of the solvent mixture changes from 20% to 50% DMSO), and those of reactions 1 and 3 (reduction of temperature from 80 °C to 60 °C). The distribution of products also appears to be unaffected by either the nature of ROH or steric hindrance of the R group on the products 2 and 3. The only determinant factor on the proportion of the products formed, seems to be the ratio of the reagents 1-ROH-KOH.

The formation of disaccharide 3 is favoured when the ratio 1-ROH-KOH = 1:1.2:2.4 (reactions 1, 5, 7 and 8). The isolated disaccharide 3 was reacted with the anhydro derivative 1 (conditions described in reaction 4), to afford the trisaccharide derivative 4 in better yields than for the reaction obtained in the one-pot reaction described in Table 1 (reaction 4). Thus, we obtained the trisaccharide derivative 4a (RZ= CH_2=CH-CH_2O-) after purification in 60% yield.

When the ratio of reagents was 1-ROH-KOH = 1:3:6, the formation of the intermediate 2 was favoured, and isolated in a good yield. The intermediate 2 has the potential to be subsequently used for the synthesis of either the disaccharide 3 and trisaccharide 4 or 5-*O*-alkyl-D-xylofuranose compounds which can be obtained after deprotection of the isopropylidene groups.9,10)

The products 2, 3 and 4 were also prepared in a one-pot synthesis using the same conditions of reaction 1 (Table 1), by replacing the anhydro-derivative 1 with either of its precursors, namely 5-*O*-tosyl-1,2-*O*-isopropylidene-α-D-xylofuranose (1') 10) or 5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose (1").11) The basic reaction media allowed the rapid formation, *in situ*, of the anhydro-derivative 1 from such precursors. Using this second procedure, we noticed that the proportions of the products 2, 3 and 4 were very close to those obtained for reaction 1 (Table 1) except that the reaction time was longer and the yields were lower. In a different study, we found that either of the derivatives 1' or 1" in the presence of NaOH in a solution of either ethanol-water [1:1, (v/v)] or dioxane-water [4:1, (v/v)], at room temperature, afforded the derivative 1 in 90% yield (the reaction time was less than 2 hours). Such an efficient and convenient access to the anhydro-derivative 1 proved advantageous for the synthesis of 3 and 4.

The compounds prepared in the present study 2, 3 and 4, provide the potential to synthesize a wide variety of novel non-ionic surfactants possessing either one or two lypophilic chains which may be of a different character. Such may be obtained following derivatisation of the free hydroxyl group on compounds of the type 3 or 4 and hydrolysis of the isopropylidene protecting groups.

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8) General Procedure for the preparation of ether-linked disaccharides 3 and trisaccharides 4 (Z= O): Finely powdered potassium hydroxide and the anhydro derivative 1 were added to a stirred solution of the appropriate ROH in toluene-DMSO, at 80 °C. After the reaction reached 90% completion (as measured by HPLC on a Merck Lichrospher 100 RP 18 column eluted with water-acetone), the reaction was filtered and the filtrate neutralized with a saturated aqueous solution of NH_4Cl. The organic phase was separated, washed with water (twice), dried (Na_2SO_4) and evaporated under reduced pressure. The syrup obtained was purified on a silica gel column eluted with hexane-ethyl ether. All products were characterised by ^{13}C-NMR spectroscopy (300MHz, internal Me_4Si) and elemental analysis.

For example, the ^{13}C-NMR spectrum ($CDCl_3$) of the xylosyl moiety of disaccharide compound 3c (RZ= $C_{12}H_{25}O$-) had the following resonances: δ C_1 $C_{1'}$ (103.8; 103.9), C_2 $C_{2'}$ (74.9; 77.0), C_3 $C_{3'}$ (77.6; 81.1), C_4 $C_{4'}$ (82.7; 84.4), C_5 $C_{5'}$ (67.4 ;66.6), $\underline{C}Me_2$ (110.7 ;110.9), $C\underline{Me}_2$ (25.1; 25.2; 25.5; 25.7).

The physical characteristics of compounds 3 were the followings:

3a $[\alpha]_D^{25}$ = -37.8° (c 1.8, $CHCl_3$) 3b $[\alpha]_D^{25}$ = +6.2° (c 1.3, $CHCl_3$)

3c $[\alpha]_D^{25}$ = -28.8° (c 1.2, $CHCl_3$) 3d $[\alpha]_D^{25}$ = -36.3° (c 1.1, $CHCl_3$)

9) Deisopropylidenation was carried out by hydrolysis with H_2SO_4 (1 N) in dioxane-H_2O [80:20, (v/v)], at 70 °C. After the reaction was 97% complete (monitored by HPLC), the solution was cooled and neutralized with a satured solution of NaOH and solid $NaHCO_3$. The filtrate was evaporated under reduced pressure and then purified by silica gel column chromatography using hexane-acetone.

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11) The iodo derivative 1" was prepared starting from 1,2-*O*-isopropylidene-α-D-xylofuranose according to the method of Plusquellec 12) in a 55% yield.

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