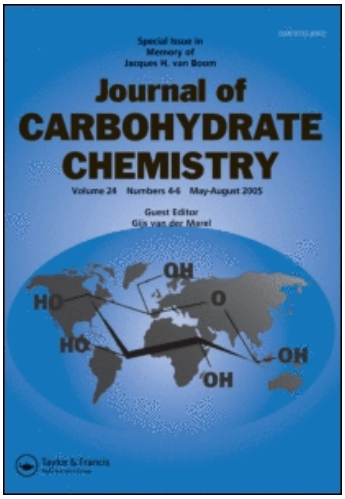

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COMMUNICATION

SYNTHESIS OF CARBOHYDRATE FORMACETAL DIMERS UNDER NON-ACIDIC CONDITIONS[1]

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The linking mode between sugar units in biopolymers such as polysaccharides or oligonucleotides has recently gained increased attention. For example, neutral analogues of phosphodiester linkages have been designed to produce modified DNA fragments[2] or nucleic acid mimics with promising properties in the control of gene expression.[3] A recent focus has been directed towards neutral and achiral linkers like ethylene glycol, propoxy[4] or longer alkyl chains[5] but also the simple methylene group.[6] In the latter case, the methylene linker was part of a formacetal moiety.

We have been interested in a general method that could easily be used for the spanning of acid-sensitive common carbohydrate moieties such as sugar acetonides, to form methylene-linked duplicates bearing new and diverse application prospects.

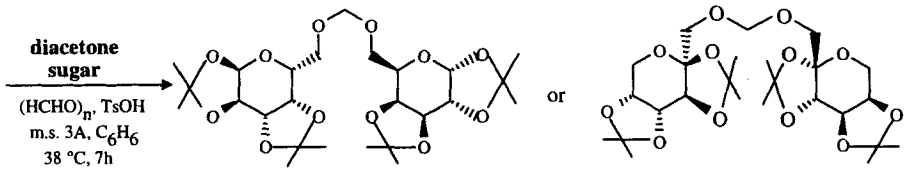
$$\text{sugar - OH} \longrightarrow \text{sugar - O - CH}_2\text{ - O - sugar}$$

The methods commonly used for the synthesis of carbohydrate formacetals are either based on a classical acid-catalyzed condensation of formaldehyde,[7] on the use of DMSO/NBS[8] or DMSO/bromine[9] systems or on alkaline procedures involving the condensation of the alcoholate with methylene dihalides.[10] In the latter method, phase-transfer catalysis was applied to produce formacetals of a few glycosides.[11,12] However successful this technique may have proven in other hands, it appeared to us somewhat less reproducible than expected, probably because of the highly critical experimental conditions prescribed.

We thus turned towards alternative methods that would be easier to perform and more widely applicable while respecting the pre-existent acetal protections in the starting materials. The sugar templates involved in the present study are the diacetonide derivatives of D-galactose, D-fructose, L-sorbose, D-glucose, and a dioxolane-protected methyl α-D-riboside.[13]

Transacetalisation from dimethoxymethane - which formed methylene-linked dimers when applied to trimethanol alkanes[14] - led to a mixture of products in the case of acetonide protected sugars.

When applying strict monitoring of the reaction process however, the preparation was successful in the case of two formacetal dimers:



1 **2**

- the D-galacto duplicate **1**, $[\alpha]_D$ -61° (CH_2Cl_2), in 68% yield[15]

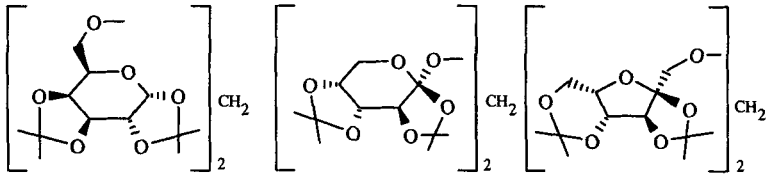
- the D-fructo duplicate **2**, mp 104 °C, $[\alpha]_D$ -20° (CH_2Cl_2), in 80% yield.[16]

When applied to other similarly protected sugars in the D-gluco, D-ribo and L-sorbo series, the same protocol resulted in extensive degradation. Further trials using either the DMSO/NBS method[15] or PTC techniques also led to disappointing results.

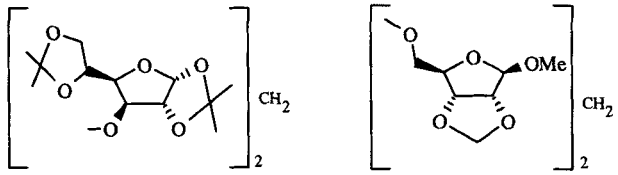
Finally we devised a convenient procedure for the synthesis of formacetal dimers **1-5** under plain basic conditions : treatment of the protected sugars with dibromomethane

and potassium hydroxide in DMSO at room temperature[17] afforded the formacetal dimers **1-5** :

- the D-galacto **1** and D-fructo **2** duplicates in 68 and 72% yield, respectively;
- the L-sorbo duplicate **3**, mp 139-40 °C, $[\alpha]_D$ -34° (CH_2Cl_2), in 63% yield;
- the D-gluco duplicate **4**, mp 86 °C, $[\alpha]_D$ -28° (CH_2Cl_2), in 90% yield;
- the D-ribo duplicate **5**, mp 73-4 °C, $[\alpha]_D$ -81° (CH_2Cl_2), in 60% yield.



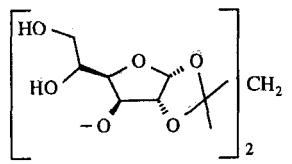
1 (D-galacto) **2** (D-fructo) **3** (L-sorbo)



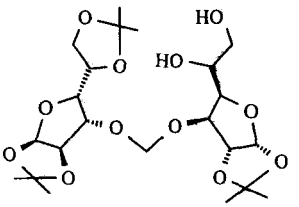
4 (D-gluco) **5** (D-ribo)

Thus, the use of cheap potassium hydroxide in DMSO allowed the synthesis of methylene-linked carbohydrate bolaform-type duplicates and the reaction was applicable to acid-sensitive compounds such as acetal protected sugars.

Next we investigated the partial and selective hydrolysis of the acetals in order to regenerate some free hydroxyl groups in the formacetal dimers. Selective hydrolysis of the 5,6-*O*-isopropylidene acetal in glucofuranose derivatives is a well-known process[5,18] which could also be successfully applied to the D-gluco duplicate **4**. Selective removal of both 5,6-*O*-acetonides in **4** was indeed attained using a 0.03 N H_2SO_4 / MeOH solution at room temperature under TLC monitoring (7 h for ca. 96 % conversion) to afford in 74% yield syrupy tetraol **6**, $[\alpha]_D$ -79° (CH_2Cl_2); ^{13}C NMR δ 91.4; ^1H NMR δ 4.86 (s) (formacetal moiety), along with 13% of the readily separable syrupy diol **7**, $[\alpha]_D$ -118° (CH_2Cl_2).[19] Under more acidic conditions or over a longer period of time, the reaction led to a mixture of polyols.



6



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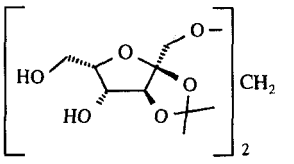

8

When treated for 0.5 h at rt with 0.27 N H_2SO_4 / MeOH, the L-sorbo duplicate **3** also underwent a clean selective hydrolysis to yield (81%) syrupy tetraol **8**, $[\alpha]_D$ +4° (CH_2Cl_2); ^{13}C NMR δ 94.8; ^1H NMR δ 4.79 (s) (formacetal moiety), along with traces of the intermediate diol.

^1H and ^{13}C NMR data for duplicates (in $CDCl_3$).

	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	$CH_2(OR)_2$
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{6a,6b}$	$J_{5,6b}$	
	C-1	C-2	C-3	C-4	C-5	C-6		C-7
1	d, 5.53	dd, 4.31	dd, 4.60	dd, 4.25	m, 3.97	dd, 3.79	dd, 3.67	s, 4.75
	5.2	2.1	7.8	1.8	5.7	10.4	7.0	
	96.4	70.7[a]	70.5[a]	66.7	71.2	66.3	-	91.9
2	m, 3.71	-	d, 4.46	dd, 4.59	dd, 4.23	dd, 3.93	bd, 3.73	s, 4.78
			2.6	7.9	1.8	13.0		
	61.2	102.6	70.1[a]	71.1	70.3[a]	68.9	-	95.7
3	s, 3.67	-	s, 4.54	d, 4.31	m, 4.11	dd, 4.06	bd, 4.00	s, 4.82
				2.2	2.0	13.0		
	60.4	97.3	84.2	72.2	73.3	67.2	-	95.6
4	d, 5.89	d, 4.59	d, 4.28	dd, 4.15	m, 4.32	dd, 4.10	dd, 4.00	s, 4.86
	3.2		3.2	7.5	6.3	8.3	5.7	
	105.3	83.1	38.8	81.1	72.6	67.2	-	92.9
5	s, 5.00	d, 4.50	bd, 4.65	m, 4.34	5a : dd, 3.64	-	-	s, 4.75
		5.8		6.6	10.3			
	106.7	81.4	84.3[a]	84.1[a]	5b : dd, 3.57 8.0 69.0			
6	d, 5.84	d, 4.48	d, 4.33	dd, 4.08	m, 3.96	m, 3.82	m, 3.65	s, 4.86
	3.8		2.6	9.8				
	105.8	82.1	78.7	79.7	68.1	64.2	-	91.4
8	s, 3.76	-	s, 4.43	m, 4.20	m, 4.09	m, 3.93	m, 3.93	s, 4.79
	61.2	112.5	86.2	76.2	80.9	61.2	-	94.8

a. Assignments may have to be reversed.

In contrast, duplicates **1** and **5** underwent selective cleavage of the inter-glycosidic methylene acetal bridge, thus giving back the protected corresponding monosaccharides. Finally, the various acetal functions of the D-fructo derivative **2** showed almost similar hydrolysis rates : no selectivity could be attained under miscellaneous experimental conditions.

The present study provides information about the relative stabilities towards acidic conditions of the acetals involved. The acyclic methylene acetal is more stable than the isopropylidene acetal formed from a primary and a secondary hydroxyl group, regardless of the ring-size - 1,3-dioxolane or 1,3-dioxane - as shown by the selective cleavage in duplicates **3** and **4**.

Depending on the sugar series they belong to and the protective array they bear, those formacetal dimers can subsequently be selectively derivatized to partially protected polyhydroxylated systems with a view to designing structures with diversified potential applications.

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16. Compounds **1-8** all gave elemental combustion analyses in accord with the proposed structures.
17. In a typical experiment, the protected sugar (1 mmol) and powdered KOH (450 mg, 8 mmol) were directly weighed in the reaction flask ; DMSO (3 mL) and dibromomethane (348 mg, 2 mmol) were added and the mixture was stirred for 4 h at rt under an argon atmosphere. After dilution with CH_2Cl_2, the organic layer was washed twice with water, then dried over $MgSO_4$. The residue obtained after solvent evaporation was purified by silica gel column chromatography (diethyl ether/petroleum ether).
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19. Significant ^1H NMR data for **7**: 3.70 (m, 2H, H-6'a and H-6'b), 3.78 (m, 2H, H-6a and H-6b), 4.01 (m, 2H, H-4 and H-4'), 4.10 (m, 2H, H-5 and H-5'), 4.27 (d, 1H, H-3, $J_{3,4}$ = 3.2), 4.35 (d, 1H, H-3', $J_{3',4'}$ = 3.2), 4.51 (d, 2H, H-2 and H-2'), 4.83 and 4.91 (AB, 2H, H-7a and H-7b, J_{gem} = 7.0), 5.85 and 5.88 (2d, 2H, H-1 and H-1', J_{vic} = 3.8).