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Introduction of a carboxyl group through an acetal as a new route to carboxylic acid derivatives of sugars

Sylvie Carbonnel, Catherine Fayet, Jacques Gelas *

École Nationale Supérieure de Chimie de Clermont-Ferrand, Ensemble Scientifique des Cézeaux, BP 187, F-63174 Aubière, France

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Abstract

A new class of carboxylic acid derivatives of sugars is described. Acetalation of mono- and disaccharides with a functionalized vinylic ether or a diethoxybutanoate afforded mono- and diacetals bearing an ester group. Their saponification led to the corresponding carboxylic acid acetals in which the length of the acetal side chain can be modulated.

Keywords: Carbohydrates; Carboxylic acid cyclic acetals

1. Introduction

It is well known that carbohydrates and particularly their carboxylic acid derivatives, like α-hydroxy acid anions, show metal complexing behaviour with inorganic salts [1]. A large number of applications of the formation of such complexes is reported in the literature: (i) in analytical–physical methods, (ii) for the separation of sugars (e.g., ion-exchange resins); (iii) in organic synthesis where the outcome of some reversible reactions can be changed by addition of cations; (iv) in biological systems where carbohydrates play a role in the transport of cations through membranes or cell walls. Salt formation from alginic acid and calcium has become of industrial importance, and complexing molecules such as gluconic and glucaric acid are efficient sequestering agents of great industrial interest in the detergent field [2]. Different methods have been developed for the synthesis of carboxylic acid derivatives of sugars [3], among them, carboxymethylation, oxidation, cyanoethylation, esterification, and copolymerization.

This report deals with the synthesis of new carboxylic acid derivatives of mono- and disaccharides, for which a carboxyl group is introduced through an acetal (Scheme 1). The synthesis of some functionalized acetals of sugars has been previously studied in our laboratory [4], as acetalation represents an easy way for effecting structural modification of carbohydrates. In the present case, carboxylic acid esters are prepared and constitute interesting synthons for further chemical modification. Lastly, the presence of the carboxylic acid group confers complexing properties, and the influence of the length of the lateral chain borne by the acetal can be studied. For this purpose, several carboxylic acid derivatives of mono- and disaccharides were prepared.

Among carboxylic acid acetals of sugars, only pyruvic acid acetals, well known to occur in many natural polysaccharides from veg-

* Corresponding author. Tel.: +33-4-7326-4110; fax: +33-4-7340-7008.

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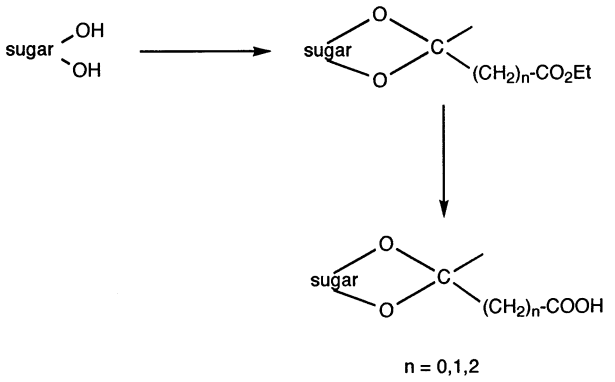


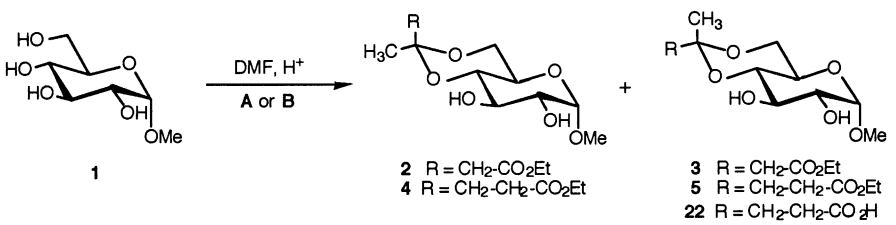
Scheme 1.

etable [5a,b], animal [5c], and bacterial [5b,d] sources, are reported in the literature. Most often 4,6-dioxane type acetals of hexopyranosyl residues, and, infrequently, dioxolane rings in the 2,3- or 3,4-positions are found [5e]. Gorin and Ishikawa [6] published the first synthesis of these compounds and determined the configuration at the acetal carbon atom. However, poor yields were reported, as a preliminary protection of the hydroxyl groups in the 1,2- and 3-positions and subsequent activation of the resulting diols were required. A more efficient route to pyruvic acid acetals starts from silylated diols [7].

2. Results and discussion

Reaction of methyl α-D-glucopyranoside (**1**) (Scheme 2) with three molar equivalents of ethyl 3-ethoxybut-2-enoate (**A**) was performed in DMF under mild acidic conditions. TLC monitoring indicated the formation of two compounds. After 24 h at 70 °C the reaction was complete, and two products were partially separated by silica gel column chromatography and identified by means of their ^{1}H and ^{13}C NMR spectra as methyl 4,6-*O*-[(*S*)-2-ethoxycarbonylpropylidene]-α-D-glucopyranoside (**2**) and methyl 4,6-*O*-[(*R*)-2-ethoxycarbonylpropylidene]-α-D-glucopyranoside (**3**). First, in each ^{13}C NMR spectrum (Table 1), a signal at 100.5 or 99.8 ppm was characteristic [8] of an acetal carbon atom included in a dioxane ring. These two different values indicated that the two possible stereoisomers on the acetal carbon atom were obtained. Furthermore, by analogy with the effects observed for pyruvic acid acetals [7,9], the configurations of the two stereoisomers could be determined. In a general way, in ^{1}H NMR spectroscopy (Table 2), protons of an axially oriented acetal methyl group are deshielded, as compared with protons of an equatorially oriented methyl group. On the other hand, in the ^{13}C NMR spectrum the carbon atom of an equatorial acetal methyl group is deshielded [7–9]. On the basis of these data, (S) and (R) configurations could be assigned unambiguously to compounds **2** and **3**, respectively.

In the same way, treatment of methyl α-D-glucopyranoside (**1**) with ethyl 4,4-diethoxypentanoate (**B**) in DMF (Scheme 2), at room temperature and in the presence of a catalytic amount of camphorsulfonic acid, afforded a 1:1 mixture of the 4,6-*O*-[3-ethoxycarbonylbutylidene] derivatives **4** and **5**. The yield was significantly increased with respect to the previously described reaction (70% versus 48%). The two compounds were separated by column chromatography, identified by



1

2 R = CH_2-CO_2Et
4 R = CH_2-CH_2-CO_2Et

3 R = CH_2-CO_2Et
5 R = CH_2-CH_2-CO_2Et
22 R = CH_2-CH_2-CO_2H

Reagent	Conditions	R	Compounds	Yield
A: H_3C-C(OEt)=CH-CO_2Et	*p*-TsOH, 70 °C	CH_2-CO_2Et	**2** (S) + **3** (R)	48%
B: H_3C-C$(OEt)_2$-CH_2-CH_2-CO_2Et	CSA, 25 °C	$(CH_2)_2$-CO_2Et	**4** (S) + **5** (R)	70%

Scheme 2.

Table 1
^{13}C NMR data ($CDCl_3$) for compounds **2–9** and **22**

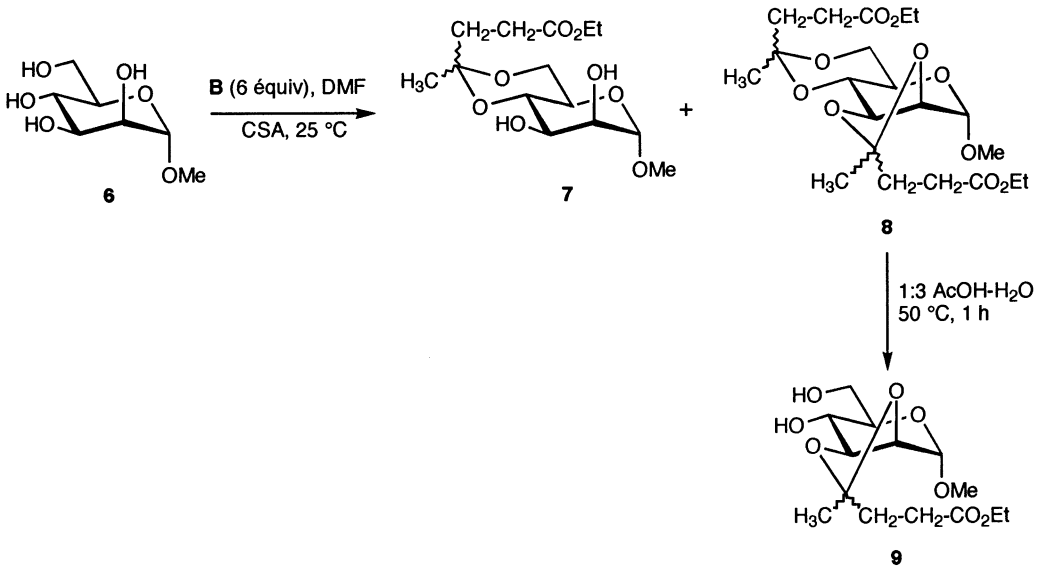
	CH_3 (OEt)	CH_3 axial	CH_3 equatorial	$(CH_2)_n$ axial	$(CH_2)_n$ equatorial	OCH_3	CH_2 (OEt)	C-6	C-2	C-3	C-4	C-5	C-1	C-7 acetalic	C=O (CO_2Et)
2 (S)	14.1		27.1	37.5		55.3	60.1	62.0	62.7, 68.8, 72.4, 74.0				99.9	98.9	169.2
3 (R)	14.1	17.7			46.8	55.3	60.6	62.3	62.9, 71.4, 72.7, 73.6				99.9	99.1	169.3
4 (S)	14.1		25.9	26.2 29.3		55.3	60.6	62.1	72.8	71.5	73.2	62.8	99.9	100.5	173.2
5 (R)	14.1	18.5			28.0 36.4	55.4	60.3	62.2	72.8	71.5	73.5	63.2	99.9	99.8	173.9
7	14.1	18.7	26.0	26.4 29.5	28.0 36.5	54.9	60.4 60.7	62.0 62.1	69.1, 75.5, 69.2 75.7, 69.5, 78.4, 78.7				101.5	100.1 100.8	173.6 174.4
9	14.2	endo/exo 23.8, 25.4		endo/exo 29.3, 34.4 29.5, 35.4		54.9	60.4 60.5 60.6	61.9 62.1 62.3	69.1, 69.2, 69.5 75.5, 75.7, 78.4, 78.7				98.3 98.4	109.9 110.3	173.2 173.8
				4,6-acetal											
	14.2	18.4	26.0	26.2	28.0		60.4							100.4	172.9
8				29.8	36.5	55.0	60.7	61.9	61.0, 61.1				98.7	100.5	173.0
				2,3-acetal				62.0	72.3, 72.5, 72.7, 74.6, 74.7				98.8		173.1
	14.2	endo/exo 23.7, 25.5		endo/exo 29.4, 29.5 34.3, 35.3			60.6 60.7		75.0, 75.9, 76.2					109.9 110.3	173.8
22 [a]		17.9			30.8 38.1	54.6		61.8	72.5	70.1	73.8	63.4	99.8	100.6	177.1

[a] Solvent: DMSO-d_6.

Table 2
^{1}H NMR data ($CDCl_3$) for compounds **2–9** and **22**

	CH_3 (OEt)	CH_3 equatorial	CH_3 axial	$(CH_2)_n$ equatorial	$(CH_2)_n$ axial	OCH_3	H-2	H-3	H-4	H-5	H-6, H-6′	CH_2 (OEt)	H-1
2	1.25 (t)	1.50 (s)			2.90 (s)	3.40 (s)	3.60 (m)	3.90 (dd)	3.60 (m); 3.80 (m)			4.10 (q)	4.70 (d)
3	1.20 (t)		1.60 (s)	2.65 (s)		3.40 (s)	3.55 (m)	3.90 (dd)	3.55 (m); 3.75 (m)			4.10 (q)	4.70 (d)
4	1.20 (t)	1.35 (s)			2.10 (m) 2.30 (m)	3.40 (s)		3.50 (m)	3.75 (m)			4.10 (q)	4.70 (d)
5	1.20 (t)		1.45 (s)	2.0 (m) 2.45 (m)		3.40 (s)		3.50 (m)		3.70 (m)		4.10 (q)	4.70 (d)
7	1.25 (t)	1.30 (s)	1.40 (s)	1.95 (m) 2.45 (m)	2.12 (m) 2.30 (m)	3.35 (s)		3.90 (m)	3.80 (m)		3.60 (m)	4.10 (m)	4.70 (d)
9	1.25 (t)	1.30 (s) endo	1.45 (s) exo	1.90 (m) 2.40 (m)	2.05 (m) 2.35 (m)	3.35 (s)	4.10 (m)		3.85 (m)		3.55; 3.70 (2m)	4.10 (m)	4.85 (s)
8	1.25 (m)	1.30 (s) 1.33 (s)	1.45 (s) 1.48 (s)	1.95 (m) 2.40 (m)	2.10 (m) 2.30 (m)	3.35 (s)	4.10 (m)		3.45–3.85 (m)			4.10 (m)	4.85 (d)
22 [a]			1.40 (s)	1.80 (m) 2.15 (m)		3.30 (s)			3.40–3.77 (m)				4.60 (s)

[a] Solvent: DMSO-d_6.

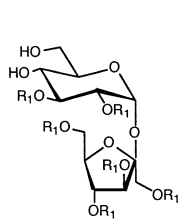


Scheme 3.

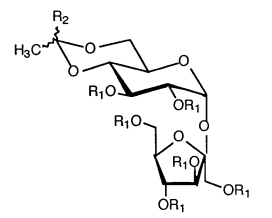
NMR spectroscopy (Tables 1 and 2), and the configuration at the acetal carbon atoms was determined as above.

The cis configuration of the hydroxyl groups in positions 2 and 3 of methyl α-D-mannopyranoside (**6**) generally allows the formation of a dioxolane-type acetal at these positions, in addition to the 4,6-acetal. The diacetal **8** was therefore obtained with the monoacetal **7** by reaction of the sugar with six molar equivalents of ethyl 4,4-diethoxypentanoate **B** (Scheme 3) in DMF at room temperature, in the presence of a catalytic amount of camphorsulfonic acid. These two compounds were easily separated by column chromatography. The major diacetal **8** (65%) was eluted first, followed by the monoacetal **7** (14%). They were identified by NMR spectroscopy. The monoacetal **7** was a mixture of the two stereoisomers at the acetal carbon atom, as indicated by signals at 100.1 and 100.8 ppm in the ^{13}C NMR spectrum (Table 1). As previously described, the signal at 18.6 ppm in the ^{13}C NMR spectrum and the one at 1.40 ppm in the ^{1}H NMR spectrum (Table 2) were assigned to the axially oriented acetal methyl group. In the same way, the signals at 20.6 ppm (Table 1) and 1.30 ppm (Table 2) were assigned to the equatorially oriented acetal methyl group. The ratio of the two stereoisomers was estimated to be 60:40 in favour of the (S) configuration. As expected, the ^{13}C NMR spectrum of **8** showed two signals at 100.4 and 100.5 ppm, corresponding to the acetal carbon atom of a 4,6-dioxane acetal. Two additional signals at 109.9 and 110.3 ppm, respectively, were characteristic [8] of the acetal carbon atom of a dioxolane ring in the 2,3-position. Compound **8** was consequently a mixture of the four possible stereoisomers for this diacetalic derivative. This was confirmed by the analysis of the spectra of the 2,3-acetal **9** obtained by selective hydrolysis of the 4,6-acetal under mild conditions, and identified as a 1:1 mixture of endo- and exo-stereoisomers (signals at 109.9 and 110.3 ppm, characteristic of a dioxolane-type acetal [8]).

Table 3



10 R_1 = Ac
13 R_1 = H



11 R_1 = Ac ; R_2 = CH_2-CO_2Et
12 R_1 = Ac ; R_2 = CH_2-CH_2-CO_2Et
23 R_1 = Ac ; R_2 = CH_2-CH_2-CO_2H

Starting compound	Reagent	Product
10	A	**11**
10	B	**12**
13	B, Ac_2O	**12**

Table 4
^{13}C NMR data ($CDCl_3$) for compounds **11–18** and **23**

	CH_3 (OEt)	CH_3 axial	CH_3 equatorial	CH_3 (OAc)	$(CH_2)_n$ axial	$(CH_2)_n$ equatorial	CH_2 (OEt)	*C*-1′ [a], *C*-6, *C*-6′	*C*-1, *C*-1′ [b]	*C*-7	*C*-2′ [a]	*C*=O
11	14.0	17.2	27.1	20.5–20.9	37.5	46.8	60.3	61.7; 61.9	90.4	98.9	103.9	168.6–170.5
	14.1						60.4	63.0; 63.2		99.3	104.0	
12	14.2	18.2	25.9	20.5–20.7	26.0	29.7	60.2	61.7; 63.1	90.2	100.0	103.8	169.7–173.5
					29.2	36.4	60.6	63.2; 63.3	90.4	100.6	104.0	
15	14.0	17.3	27.1	20.4–20.9	37.4	46.6	60.3	61.7; 61.9	91.6; 92.0	99.1		168.5–170.5
	14.1						60.6	62.1	93.2; 93.3	99.5		
16	14.2	18.1	25.9	20.4–20.7	26.0	27.9	60.3	61.7	91.6; 91.9	100.1		169.4–173.4
					29.1	36.4	60.6	61.8	92.9; 93.2	100.7		
18	14.1	18.1	25.9	20.4–20.7	25.9	27.9	60.3	61.7	92.3	100.0		169.3–173.4
					29.1	36.4	60.6	61.8	92.5	100.7		
23		18.3	26.0	20.5–21.0	25.9	27.7		62.1; 62.9	90.4; 90.5	99.9	103.9	177.7
					28.9	36.2		63.1; 63.4		100.6	104.1	177.9

[a] For sucrose only.
[b] For trehalose only.

Table 5
^{1}H NMR data ($CDCl_3$) for compounds **11–18** and **23**

	CH_3 (OEt)	CH_3 equatorial	CH_3 axial	CH_3 (OAc)	$(CH_2)_n$ equatorial	$(CH_2)_n$ axial	*H*-4,4′, *H*-5,5′ *H*-6,6′	*H*-2,2′, *H*-3,3′	CH_2 (OEt)	*H*-1,1′
11	1.20 (t)	1.45 (s)	1.60 (s)	2.05–2.15	2.60 (s)	2.90 (dd)	3.75 (m); 3.95 (m) 4.20 (m)	4.75 (m) 5.35 (m)	4.10 (q)	5.60 (d)
12	1.20 (m)	1.36 (s)	1.40 (s)	1.95–2.10	2.15 (m)		3.60–4.05 (m)	4.75 (m) 5.25–5.45	4.10 (q)	5.60 (d)
15	1.25 (t)	1.45 (s)	1.60 (s)	2.05 (m)	2.60 (s)	2.85 (dd)	3.75 (m); 4.20 (m); 5.20 (m); 5.30 (m)	5.00 (m)	4.10 (q)	5.40 (m)
16	1.20 (t)	1.25 (s)	1.40 (s)	2.0 (s) 2.10 (s)	1.90; 2.25; 2.30 2.40 (m)		3.70–4.0 (m)	4.90;5.15;5.30 (m)	4.10 (q)	5.45 (m)
18	1.20 (t)	1.25 (s)	1.40 (s)	2.02 (s) 2.10 (s)	1.90; 2.25; 2.30 2.40 (m)		3.70–4.00 (m) 5.75 (m)	4.85 (m)	4.10 (q)	5.85 (m)
23		1.30 (s)	1.45 (s)		1.90–2.50 (m)		3.60–4.30 (m)	4.80 (dd) 5.30–5.45 (m)		5.62 (d)

These syntheses were then extended to certain disaccharides that are particularly interesting in the detergent and complexation fields due to their large number of hydroxyl groups. Acetals of disaccharides have already been synthesized in our laboratory [4], but to our knowledge, the synthesis of carboxylic acid acetals derived from disaccharides has not been developed. Starting from the 4,6-silylated diol of sucrose, we have shown [10] that 1′,2,3,3′,4′,6′-hexa-*O*-acetyl-4,6-*O*-(1-ethoxycarbonylethylidene)sucrose could be prepared according to the method of Hashimoto et al. [7].

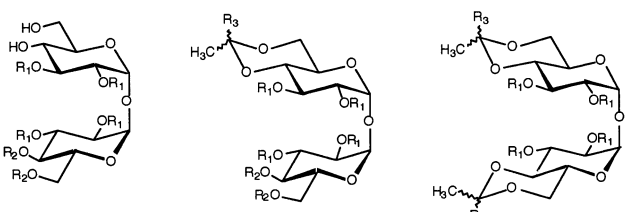
Reaction of 1′,2,3,3′,4′,6′-hexa-*O*-acetyl sucrose (**10**), prepared as described previously [11], with the vinylic ether (**A**) (Table 3), was carried out in acetonitrile. After 20 h at room temperature, TLC indicated the formation of only one compound that was purified by silica gel chromatography and characterized by NMR spectroscopy (Tables 4 and 5). In the ^{13}C NMR spectrum, two signals at 98.9 and 99.3 ppm were observed, corresponding to the new acetal carbon atom of compound **11**, which was thus shown to be a mixture of the two possible stereoisomers. This was confirmed by the presence of acetal methyl group signals at 37.5 ppm (axial position) and 46.8 ppm (equatorial position). A similar treatment of 2,2′,3,3′,4′,6′-hexa-*O*-acetyl-α,α-trehalose (**14**) [12] afforded in 35% yield the expected 4,6-acetal of trehalose **15** as a 1:1 mixture of the two stereoisomers (Table 6).

However, direct condensation of ethyl 3-ethoxybut-2-enoate (**A**) with sucrose (**13**) was unsuccessful. Starting from trehalose (**19**) (Table 6), the reaction afforded a single compound, identified as compound **15** through its transformation into the peracetylated derivative. The yield was poor (10%) and could not be improved. The low reactivity of **A** could be attributed to the proximity of the carboxyl group with regard to the vinyl ether function. More drastic conditions could be required but they are incompatible with the presence of the glycosidic bond. It is reported in the literature [6,7] that the synthesis of pyruvic acid acetals is also difficult to realize and has only been achieved after protection of the starting material in multistep procedures with poor yields.

Treatment of the two partially protected derivatives **10** and **14** with ethyl 4,4-diethoxypentanoate (**B**) led in good yields to compounds **12** and **16**, respectively (Tables 3 and 6). In the ^{13}C NMR spectra of **12** and **16** (Table 4), the signals at 100.0 and 100.6 ppm were unambiguously assigned to the acetal carbon atom of the two possible isomers. Both acetal methyl groups, in axial and equatorial positions, gave distinct signals at 18.2 and 25.9 ppm, respectively. Furthermore, the diacetal **18** could be obtained starting from 2,2′,3,3′-tetra-*O*-acetyl-α,α-trehalose (**17**) [12] (Table 6). A large excess of the reagent **B** was necessary. The ^{1}H NMR spectrum (Table 5) indicated the presence of a diacetal derivative; carbon atoms C-1 and C-1′ gave only two signals with very similar shifts because of the symmetry of the molecule. But signals for both axially and equatorially oriented acetal side chains were observed. Compound **18** was thus a mixture of the three possible stereoisomers.

Transacetalation involving unprotected sucrose **13** was achieved in DMF at room temperature with three molar equivalents of **B** and camphorsulfonic acid as the catalyst (Table 3). The reaction time was reduced and the yield was increased when the ethyl alcohol produced during the acetalation was continuously removed under reduced pressure. The resulting mixture was subsequently acetylated, and the products were separated. The major

Table 6



Starting compound	Reagent (mol equiv)	Product
14	A (2)	**15**
14	B (3)	**16**
17	B (4)	**18**
19	A (3)	**15**
19	B (2; 6)	**16**, **18**

Table 7
Transacetalation of trehalose

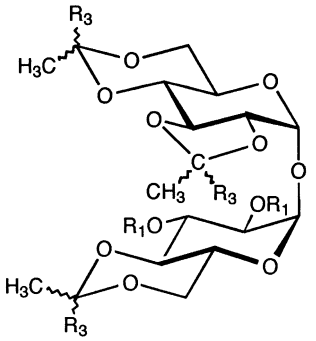
Reagent (mol equiv)	Monoacetal **16** (% yield)	Diacetal **18** (% yield)
2	42	14
4	32	18
6	10	39

compound gave ^{13}C and ^{1}H NMR spectra identical to those of **12** (Tables 4 and 5). Selectivity was slightly different: a 60:40 ratio of the two stereoisomers was observed, in favour of the (S) configuration.

Direct acetalation of trehalose (**19**) was also possible (Table 6). Two or six equivalents of **B** were added in order to favour either a mono- or a diacetalation (Table 7). The resulting compounds were identified in their peracetylated form by NMR spectroscopy (Tables 4 and 5); they were identical to **16** and **18**, respectively.

Attempting the same reaction, but using ten molar equivalents of **B**, allowed us to observe the formation of a product that eluted faster than the diacetal derivative, whereas no monoacetal was observed. The ^{13}C NMR spectrum of this new compound **20** showed the characteristic signals of the 4,6- and 4′,6′-acetals, and two additional shifts at 112.2 and 112.3 ppm, which are characteristic of an acetal carbon atom in a dioxolane ring at the 2,3 position (or 2′,3′ position). Furthermore, four signals at 24.6, 25.1, 34.5, and 34.9 ppm could be attributed to methyl and methylene acetal groups (endo/exo). In the case of its 2,3-acetylated derivative (**21**), the ^{1}H NMR spectrum showed a doublet of doublets at 4.85 ppm and a triplet centered at 5.35 ppm, which are characteristic of H-2 and H-3, respectively. On the basis of these NMR data, and by comparison with the data described by Wallace and Minnikin [13] for the tri-*O*-cyclohexylidene derivatives of α,α-trehalose, we propose for **20** and **21** the structure as a 2,3:4,6:4′,6′-triacetal (Scheme 4).

Finally, preparation of the carboxylic acid acetals corresponding to the esters described above, was achieved by employing a recently published procedure [9] carried out in aqueous potassium hydroxide at 40 °C. Thus, methyl 4,6-*O*-[(*R*)-3-carboxybutylidene]-α-D-glucopyranoside (**22**) and 1′,2,3,3′,4′,6′-hexa-*O*-acetyl-(3-carboxybutylidene)sucrose (**23**) were obtained starting from compounds **5** and **12**, respectively (for NMR data, see Tables 1, 2, 4 and 5).



20 $R_1 = H$ $R_3 = CH_2\text{-}CH_2\text{-}CO_2Et$
21 $R_1 = Ac$ $R_3 = CH_2\text{-}CH_2\text{-}CO_2Et$

Scheme 4.

In conclusion, this study shows that acetalation provides an easy method for the synthesis of carboxylic acid derivatives of sugars, and a new class of mono- and disaccharide acetals is described. Acetalations achieved with vinylic ethers confirm the interest of the method previously described by Gelas and Horton [14]. All reactions were regioselective. The ester derivatives are expected to receive much attention as useful intermediates for further chemical modifications and sugar functionalization. The spatial characteristics of the carboxylic acid acetal derivatives, which depend on the length of the acetal side chain, and their propensity to complex formation, should be studied.

3. Experimental

General methods.—Solvents were freshly distilled prior to use and dried over molecular sieves. Evaporations were performed at reduced pressure. Column chromatography was carried out with Silica Gel 60 (E. Merck, 70–230 mesh), and TLC was carried out on precoated plates (E. Merck, 5724), with detection by charring with H_2SO_4 (10% in EtOH). Melting points were determined on a Büchi SMP-20 apparatus and are not corrected. Op-

tical rotations were measured on a Jasco DIP-370 polarimeter in 1 dm tubes. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AC 400 spectrometer. Chemical shift data are given in ppm measured downfield from internal Me_4Si, and spin–spin coupling constants are in Hz. Elemental analyses were carried out by the Service Central d'Analyses du CNRS in Lyon, France.

Preparation of ethyl 3-ethoxybut-2-enoate (**A**) *[15].*—To a solution of ethyl acetoacetate (25.3 mL, 200 mmol) in abs EtOH (30 mL) were added triethyl orthoformate (32.9 mL, 200 mmol) and *p*-toluenesulfonic acid (20 mg). The mixture was heated to 65 °C, and ethyl formate was distilled as it was formed. Neutralization with NEt_3 and removal of the solvent under reduced pressure led to a residue that was distilled under vacuum to afford **A** (15.8 g, 50%) as colourless crystals: mp 29–30 °C. ^{1}H NMR ($CDCl_3$): δ 1.20 (m, 3 H, $COOCH_2CH_3$), 1.30 (t, 3 H, OCH_2CH_3), 2.25 (s, 3 H, CH_3), 3.75, 4.05 (q, 2 H, $COOCH_2CH_3$), 4.95 (s, 1 H, C=CH). ^{13}C NMR ($CDCl_3$): δ 14.1 (OCH_2CH_3), 19.0 (CH_3), 59.1, 63.6 (OCH_2CH_3), 91.0 (C=CH), 167.9 (C=CH), 172.2 (C=O).

Preparation of ethyl 4,4-diethoxypentanoate (**B**) *[15].*—To a solution of ethyl levulinate (28.4 mL, 200 mmol) in abs EtOH (30 mL) were added triethyl orthoformate (32.9 mL, 200 mmol) and 20 mg of *p*-toluenesulfonic acid. The solution was heated to 145 °C, and ethyl formate was distilled. After neutralisation with NEt_3 and evaporation of the solvent, **B** was obtained as a pale-yellow oil (41.0 g, 94%) that could be used in subsequent reactions without any further purification. ^{1}H NMR ($CDCl_3$): δ 1.10 (t, 3H, OCH_2CH_3, *J* 7.1 Hz), 1.20 (t, 6 H, $COOCH_2CH_3$, CH_3–C), 1.90, 2.28 (2m, 4 H, –CH_2–CH_2–, *J* 4.0 Hz), 3.40 (q, 2 H, OCH_2CH_3, *J* 7.1 Hz), 4.05 (q, 2 H, $COOCH_2CH_3$). ^{13}C NMR ($CDCl_3$): δ 14.1, 15.3 (OCH_2CH_3), 21.8 (CH_3), 29.7, 32.4 (–CH_2–CH_2–), 55.5 (OCH_2CH_3), 60.2, 60.4 ($COOCH_2CH_3$), 100.6 (C-3), 173.3 (C=O).

*Methyl 4,6-*O*-[(S)-2-ethoxycarbonylpropylidene]-α-*D*-glucopyranoside* (**2**) *and methyl 4,6-*O*-[(R)-2-ethoxycarbonylpropylidene]-α-*D*-glucopyranoside* (**3**).—In a round-bottom flask containing 1.00 g (5.15 mmol) of methyl α-D-glucopyranoside in 20 mL of anhyd DMF were added 3 mol equiv of **A** (2.40 g, 15.4 mmol) and a catalytic amount of *p*-toluenesulfonic acid. The mixture was heated to 70 °C for 20 h, and the reaction was monitored by TLC (EtOAc). Then $NaCO_3$ was added, and the solution was centrifuged and filtered. The solvent was evaporated under vacuum. The mixture was purified by silica gel chromatography (EtOAc), and compounds **2** and **3** were partially separated (756 mg, 48%). Data for **2**: $[\alpha]_D^{20}$ +78° (*c* 1.0, $CHCl_3$); data for **3**: $[\alpha]_D^{20}$ +52° (*c* 1.0, $CHCl_3$). For ^{13}C NMR and ^{1}H NMR data, see Tables 1 and 2. Anal. Calcd for $C_{13}H_{22}O_8$: C, 50.97; H, 7.24. Found: C, 51.12; H, 7.33.

*Methyl 4,6-*O*-[(S)-3-ethoxycarbonylbutylidene]-α-*D*-glucopyranoside* (**4**) *and methyl 4,6-*O*-[(R)-3-ethoxycarbonylbutylidene]-α-*D*-glucopyranoside* (**5**).—To 1.00 g (5.15 mmol) of methyl α-D-glucopyranoside dissolved in DMF (15 mL) were added at room temperature (rt) 2 mol equiv (2.25 g, 10.3 mmol) of reagent **B** and 20 mg of *p*-toluenesulfonic acid. TLC monitoring (EtOAc) showed the formation of two compounds (R_f 0.37 and 0.41, respectively) and no additional evolution of product was observed after 5 h. The mixture was then neutralized by addition of NEt_3 (2 mL). The solvent was evaporated under vacuum, and the crude mixture was purified on a silica gel column (EtOAc) to give 1.15 g (70%). Compounds **4** and **5** were partially separated. Data for **4**: $[\alpha]_D^{20}$ +64° (*c* 1.0, $CHCl_3$); data for **5**: mp 119–120 °C; $[\alpha]_D^{20}$ +71° (*c* 1.0, $CHCl_3$). For ^{13}C NMR and ^{1}H NMR data, see Tables 1 and 2. Anal. Calcd for $C_{14}H_{24}O_8$: C, 52.49; H, 7.55. Found: C, 52.82; H, 7.68.

*Methyl 4,6-*O*-(3-ethoxycarbonylbutylidene)-α-*D*-mannopyranoside* (**7**) *and methyl 2,3:4,6-di-*O*-(3-ethoxycarbonylbutylidene)-α-*D*-mannopyranoside* (**8**).—To a solution of methyl α-D-mannopyranoside (1.00 g, 5.15 mmol) in dry DMF (15 mL), 6 mol equiv of **B** (6.75 g, 30.9 mmol) were introduced in the presence of camphorsulfonic acid as the catalyst, in 2 h. The mixture was kept under stirring at rt for 24 h. Usual workup (neutralization and evaporation of the DMF) and chromatography (3:1 EtOAc–hexane) gave the monoacetal **7** (231 mg, 14%), and the diacetal **8** contami-

nated by **B**. A further purification in the same eluent provided pure **8** (1.49 g, 65%), as a colourless oil. Data for **8**: $[\alpha]_D^{20}$ +7° (*c* 1.0, $CHCl_3$). For ^{13}C NMR and ^1H NMR data, see Tables 1 and 2. Anal. Calcd for $C_{21}H_{34}O_{10}$: C, 56.4; H, 7.67. Found: C, 56.53; H, 8.20.

Methyl 2,3-O-(3-ethoxycarbonylbutylidene)-α-D-mannopyranoside (**9**).—A solution of the diacetal **8** (850 mg, 1.90 mmol) in 1:3 AcOH–H_2O (20 mL) was stirred at 50 °C for 1 h. The solution was then cooled and lyophilized, and the crude product was evaporated several times with MeOH. After purification by column chromatography, compound **9** (250 mg, 41%) was isolated as a colourless syrup. Data for **9**: $[\alpha]_D^{20}$ +19° (*c* 1.0, $CHCl_3$). For ^{13}C NMR and ^1H NMR data, see Tables 1 and 2.

1′,2,3,3′,4′,6′-Hexa-O-acetyl-4,6-O-(2-ethoxycarbonylpropylidene)sucrose (**11**).—To 400 mg (0.67 mmol) of the diol **10** dissolved in MeCN (8 mL) were added 310 mg (3 mol equiv, 2.01 mmol) of reagent **A** and 50 mg of *p*-toluenesulfonic acid. After 24 h at rt, TLC (1:1 EtOAc–hexane) indicated no additional evolution of product. The reaction was stopped by addition of Na_2CO_3, followed by centrifugation, filtration and evaporation of the solvent. The crude product was purified by column chromatography (1:1 EtOAc–hexane) to give **11** (156 mg, 33%) as a white syrup. For ^{13}C NMR and ^1H NMR data, see Tables 4 and 5. Anal. Calcd for $C_{30}H_{42}O_{19}$: C, 50.99; H, 5.99. Found: C, 50.89; H, 6.03.

2,2′,3,3′,4′,6′-Hexa-O-acetyl-4,6-O-(2-ethoxycarbonylpropylidene)-α,α-trehalose (**15**).—The starting diol **14** (1.00 g, 1.68 mmol) was dissolved in MeCN (20 mL) at rt, and 2 mol equiv of the vinylic ether **A** (530 mg, 3.36 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added under vigorous stirring. After 24 h, an additional 2 equiv were introduced. After 48 h, neutralization of the mixture with NEt_3 (2 mL) and usual treatment (purification by chromatography with 1:1 EtOAc–hexane) gave **15** (415 mg, 35%) as a white solid. Data for **15**: mp 70–72 °C; $[\alpha]_D^{20}$ +75° (*c* 1.0, $CHCl_3$). For ^{13}C NMR and ^1H NMR data, see Tables 4 and 5. Anal. Calcd for $C_{30}H_{42}O_{19}$: C, 50.99; H, 5.99. Found: C, 50.67; H, 6.01.

Acetalation of α,α-trehalose **19**.—A similar treatment of trehalose (1.00 g, 3.00 mmol) with 3 mol equiv of **A** under mild acidic conditions, followed by acetylation, led to compound **15** (206 mg, 10%).

1′,2,3,3′,4′,6′-Hexa-O-acetyl-4,6-O-(3-ethoxycarbonylbutylidene)sucrose (**12**)

(a) Acetalation of **10**. To 300 mg (0.50 mmol) of the diol **10** in MeCN (10 mL) were added 3 mol equiv of **B** (330 mg, 1.50 mmol) and a catalytic amount of camphorsulfonic acid. The reaction proceeded for 2.5 h at rt, and the mixture was then neutralized with NEt_3. The crude product was purified by column chromatography (1:1 EtOAc–hexane). Compound **12** (240 mg, 65%) was obtained as a syrup. Data for **12**: $[\alpha]_D^{20}$ −88° (*c* 1.0, $CHCl_3$). For ^{13}C NMR and ^1H NMR data, see Tables 4 and 5. Anal. Calcd for $C_{31}H_{44}O_{19}$: C, 51.67; H, 6.15. Found: C, 51.77; H, 6.28.

(b) Acetalation of sucrose **13**. Sucrose (1.00 g, 2.92 mmol) was suspended in anhyd DMF (15 mL) at 40 °C. The reaction proceeded at rt in the presence of 2 mol equiv of **B** and a catalytic amount of camphorsulfonic acid during 2.5 h under reduced pressure. NEt_3 was then added, and the solvent was removed in vacuo. The crude mixture was then acetylated under the usual conditions (2:1 Py–Ac_2O, 0 °C overnight, then neutralisation with an ice–Na_2CO_3 mixture, extraction with CH_2Cl_2, washing with a satd $NaHCO_3$ solution and drying over Na_2SO_4). Column chromatography (1:1 EtOAc–hexane) afforded compound **12** (778 mg, 37% yield). Physical and spectral data were identical to those described above.

2,2′,3,3′,4′,6′-Hexa-O-acetyl-4,6-O-(3-ethoxycarbonylbutylidene)-α,α-trehalose (**16**) *and 2,2′,3,3′-tetra-O-acetyl-4,6:4′,6′-di-O-(3-ethoxycarbonylbutylidene)-α,α-trehalose* (**18**)

(a) Preparation of **16** *from diol* **14**. To a solution of 300 mg (0.50 mmol) of diol **14** in MeCN (10 mL), 3 mol equiv (330 mg, 1.50 mmol) of **B** and 20 mg of camphorsulfonic acid were added. One additional mol equiv of **B** was added after 4 h in order to lead the reaction to completion. The resulting acetal **16** was isolated (320 mg, 89%) after column chromatography (1:1 EtOAc–hexane). Data for **16**: mp 57–58 °C. $[\alpha]_D^{20}$ +90° (*c* 1.0, $CHCl_3$). For ^{13}C NMR and ^1H NMR data, see Tables 4 and 5. Anal. Calcd for $C_{31}H_{44}O_{19}$: C, 51.67; H, 6.15. Found: C, 51.65; H, 6.23.

(b) Preparation of **18** *from* **17**. Compound **17** (300 mg, 0.58 mmol) was dissolved in 10 mL of 1:1 DMF–CH_3CN, **B** (510 mg, 4 mol equiv, 2.32 mmol) and a catalytic amount of camphorsulfonic acid were added and the solution was kept under stirring at rt. After 1 h, 1 mol equiv of **B** was added, and the mixture was heated at 70 °C. After 2 h, usual workup and purification by column chromatography (3:1 EtOAc–hexane) led to **18** as a white powder (222 mg, 50%). Data for **18**: mp 60–61 °C; $[\alpha]_D^{20}$ +89° (*c* 1.0 $CHCl_3$). For ^1H and ^{13}C NMR data, see Tables 4 and 5. Anal. Calcd for $C_{34}H_{50}O_{19}$: C, 53.50; H, 6.60. Found: C, 53.80; H, 6.78.

(c) Transacetalation of α,α*-trehalose* **19**. A solution containing 1.00 g (2.92 mmol) of trehalose in DMF (10 mL), 2 or 6 mol equiv of **B** and camphorsulfonic acid, was heated to 70 °C. Progress of the reaction was monitored by TLC (12:3:2 EtOAc–EtOH–H_2O). After 1.5 h, the solution was neutralized with NEt_3, and the solvent was evaporated. Acetylation under the usual conditions, followed by purification on silica gel column (1:1 EtOAc–hexane), afforded first the diacetal **18**, and then the monoacetal **16** (Table 7).

2,3:4,6:4′,6′-Tri-O-*(3-ethoxycarbonylbutylidene)*-α,α*-trehalose* (**20**) *and 2′,3′-di*-O-*acetyl-2,3:4,6:4′,6′-tri*-O-*(3-ethoxycarbonylbutylidene)*-α,α*-trehalose* (**21**).—To a solution containing 1.00 g (2.92 mmol) of **19** in 10 mL of anhyd DMF were added 6.60 g (10 mol equiv) of ethyl 4,4-diethoxybutanoate **B** and 20 mg of camphorsulfonic acid. The mixture was stirred at 70 °C for 4 h, then neutralized by NEt_3 (1 mL), and the solvent evaporated under reduced pressure. The crude residue was purified by chromatography (2:1 EtOAc–hexane). A further purification was necessary to separate **20** from reagent **B**. Thus, 486 mg (23%) of **20** were obtained. Acetylation of **20** (200 mg) with Ac_2O–pyridine led after chromatographic purification (1:3 EtOAc–hexane) to compound **21** (134 mg, 60%).

Data for **21**: $[\alpha]_D^{20}$ +83° (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 5.35 (t, 1 H, H-3′, $J_{2',3'} = J_{3',4'} = 9.5$), 5.25 (m, 2 H, H-1,1′, $J_{1',2'} = 4.4$), 4.87 (dd, 1 H, H-2′), 4.10 (m, 4 H, H-4,4′,5,5′), 3.70 (m, 10 H, H-6,6′,6″,6‴, $COOCH_2CH_3$), 2.50–1.80 (m, 18 H, OAc, $-CH_2-CH_2-$), 1.50–1.10 (m, 18 H, CH_3–acetal, $CO_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$): δ 172.9–173.7 (C=O ester), 169.1–170.4 (OAc), 112.2, 112.3 (C-8), 100.0, 100.7 (C-7,7′), 92.5, 92.8 (C-1,1′), 60.4–62.1 (C-6,6′, $COOCH_2CH_3$), 36.4, 34.9, 34.5, 29.1, 27.9, 25.9 (CH_2–C–acetal), 25.9, 25.1, 24.6, 18.1 (CH_3–acetal), 20.4–20.7 ($CO_2CH_2CH_3$).

Methyl 4,6-O-*[*(R)*-3-carboxybutylidene]*-α-D-*glucopyranoside* (**22**).—Compound **4** (512 mg) was dissolved in 16 mL of 0.2 M KOH. EtOH was distilled as it was formed. The solution was maintained at 40 °C for 35 min and then cooled to rt. Neutralization of the mixture by adding Amberlite IR-120 (H^+) ion-exchange resin, followed by filtration and lyophilisation, afforded compound **22** (480 mg, 94%). Data for **22**: $[\alpha]_D^{20}$ +45° (*c* 1.0 H_2O). For ^{13}C NMR and ^1H NMR data, see Tables 1 and 2.

1′,2,3,3′,4′,6′-Hexa-O-*acetyl-4,6*-O-*(3-carboxybutylidene)sucrose* (**23**).—Deacetylation of **12** according to the Zemplén procedure was carried out as follows. Compound **12** was dissolved in anhyd MeOH (7 mL), and a catalytic amount of a freshly prepared 0.2 M solution of MeONa was slowly added. After 2 h under stirring at rt, the starting material was entirely transformed. The solvent was evaporated under reduced pressure, and the residue was dissolved in 0.2 M KOH (10 mL). The solution was maintained under stirring at 40 °C and neutralised after 1 h with Amberlite IR-120 (H^+). Lyophilization and subsequent acetylation gave a crude mixture which was purified by column chromatography to afford **23** as a colourless oil. Data for **23**: $[\alpha]_D^{20}$ +15° (*c* 1.0, H_2O). For ^{13}C NMR and ^1H NMR data, see Tables 4 and 5.

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