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Synthesis of dispirodioxanyl pseudo-oligosaccharides by selective protonic activation of isomeric glycosylfructoses in anhydrous hydrogen fluoride †,‡

Jacques Defaye * and José Manuel García Fernández *,[1]

CNRS and CEA, Département de Recherche Fondamentale sur la Matière Condensée / SESAM, Centre d'Etudes de Grenoble, BP 85 X, F-38041 Grenoble (France)

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ABSTRACT

Dispirodioxanyl pseudotetrasaccharides 6-*O*-α-D-glucopyranosyl-α-D-fructofuranose 6-*O*-α-D-glucopyranosyl-β-D-fructofuranose 1,2′:2,1′-dianhydride, 5-*O*-α-D-glucopyranosyl-α-D-fructopyranose 5-*O*-α-D-glucopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride, 4-*O*-α-D-glucopyranosyl-α-D-fructofuranose 4-*O*-α-D-glucopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride, 4-*O*-β-D-galactopyranosyl-α-D-fructofuranose 4-*O*-β-D-galactopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride, and 3-*O*-α-D-glucopyranosyl-α-D-fructofuranose 3-*O*-α-D-glucopyranosyl-β-D-fructofuranose 1,2′:2,1′-dianhydride were respectively obtained, on a preparative scale, by dissolution of the isomeric glycosylfructoses palatinose, leucrose, maltulose, lactulose, and turanose in anhydrous hydrogen fluoride. The reaction, involving selective protonation at the free anomeric position of the fructose unit, was extended to the preparation of the pseudotrisaccharides 6-*O*-α-D-glucopyranosyl-α-D-fructofuranose β-D-fructopyranose 1,2′:2′,1-dianhydride from palatinose and fructose, and to its 3-*O*-, 4-*O*-, and 4′-*O*-glucosyl analogues using turanose and maltulose as the disaccharide precursor. The cross-reactions of palatinose with maltulose and with leucrose resulted in the preparation of 6-*O*-α-D-glucopyranosyl-α-D-fructofuranose 4-*O*-α-D-glucopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride and 6-*O*-α-D-glucopyranosyl-α-D-fructofuranose 5-*O*-α-D-glucopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride, respectively.

1. INTRODUCTION

Glucosylated difructose dianhydrides were first obtained[2] by transglucosylation reactions from maltose to difructose dianhydrides in the presence of various

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* Corresponding authors.

[1] Present address: Departamento de Química Orgánica, Faculdad de Química, Universidad de Sevilla, E-41071 Sevilla, Spain.

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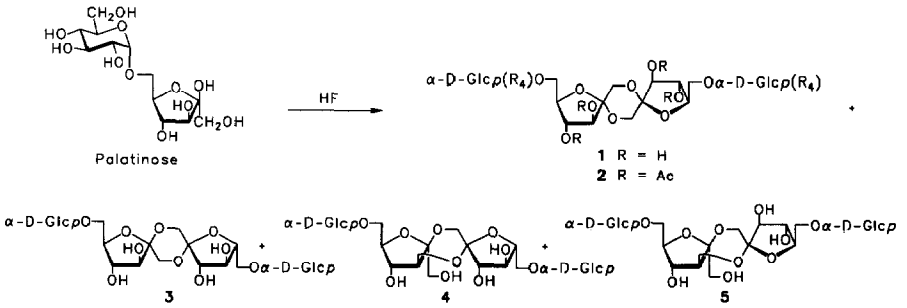
α-glucosidases. Such pseudo-oligosaccharide structures were also found in the complex oligosaccharide mixture resulting from heat treatment of palatinose in the presence of citric acid[3]. Recently, a more straightforward synthetic scheme was reported[4], involving the reaction of isomeric glycosylfructoses such as palatinose, leucrose, maltulose, turanose, and lactulose in pyridinium poly(hydrogen fluoride). A number of isomeric glycosylfructose dianhydrides were thus obtained, and it was shown that increase in the protonic strength of the reagent, by modification of the relative proportion of hydrogen fluoride (HF) in pyridine, resulted in the formation of a set of compounds ranging, within a series, from the expected kinetic products at low protonic strength, to thermodynamic products corresponding to the known[5–7] stereoelectronic control of the reaction.

More recent results have shown[1] that selective protonic activation of 1-*O*-α-D-glucopyranosyl-D-fructose (trehalulose) could be achieved in anhydrous HF, at the anomeric site of D-fructose, without affecting the glucosidic linkage. In view of the interest in glycosyl difructose dianhydrides[8,9], it was anticipated that this activation process could be extended to other glycosylfructoses, resulting in improved methods of access to glycosyl spirodioxanyl pseudo-oligosaccharides from commercially available materials. The success of this approach has further led to the synthesis of difructose dianhydrides substituted at various sites with D-glucose residues, of interest among others for the characterization of the oligosaccharide mixture formed by protonic activation of sucrose[8,10]. These syntheses have been accomplished via the cross reactions of selected isomeric glycosylfructoses, or of glycosylfructoses and D-fructose.

RESULTS AND DISCUSSION

Dissolution of two parts by weight of palatinose (6-*O*-α-D-glucopyranosyl-D-fructofuranose; isomaltulose) in one volume of anhydrous HF resulted in the almost instantaneous formation of 6-*O*-α-D-glucopyranosyl-α-D-fructofuranose 6-*O*-α-D-glucopyranosyl-β-D-fructofuranose 1,2′:2,1′-dianhydride[4] (**1**, Scheme 1), as seen from a ^{13}C NMR spectrum (Fig. 1A) of the crude reaction product, which was



Scheme 1. Products formed by the action of anhydrous HF on palatinose.

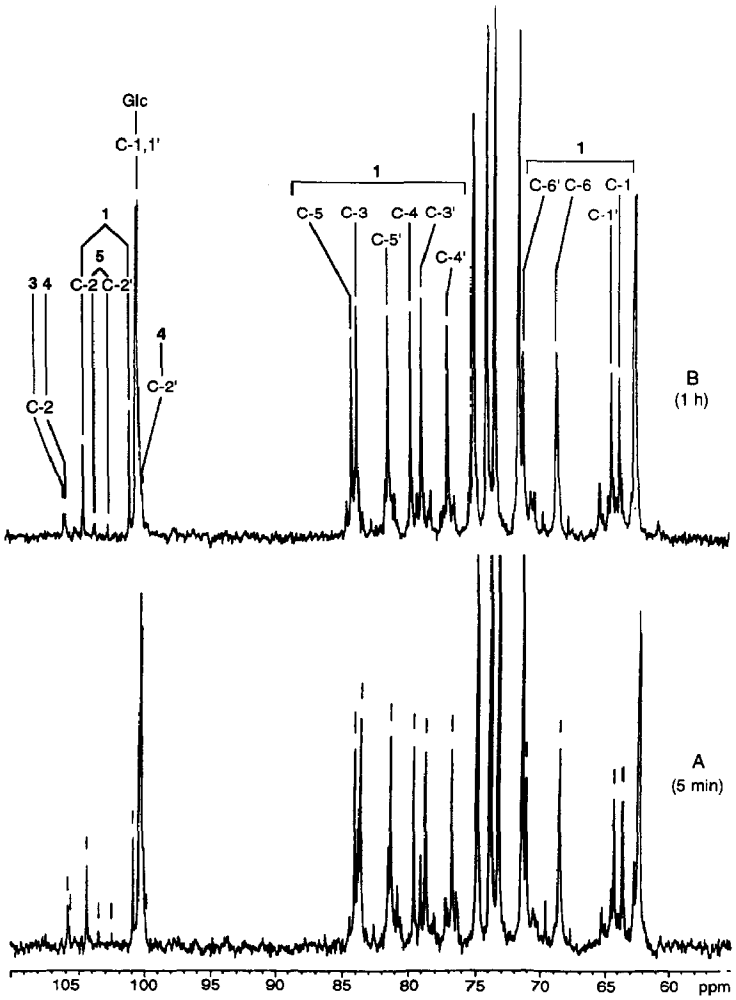
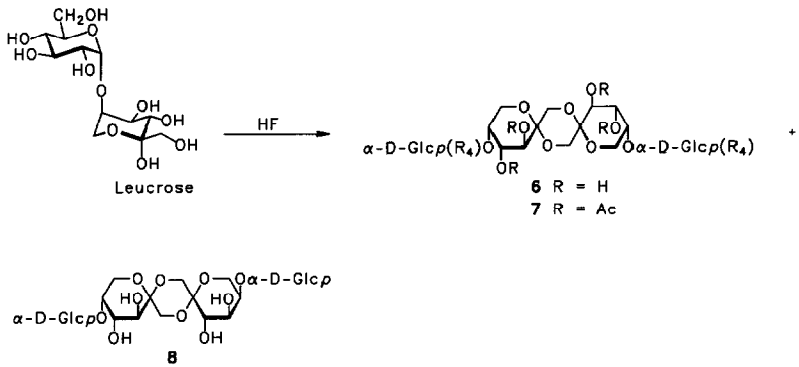


Fig. 1. Partial ^{13}C NMR spectra (50.3 MHz, D_2O) of the crude product mixture arising from the action of anhydrous HF on palatinose after 5 min and 1 h, respectively.

obtained after 5 min by ether addition to the HF solution. Minor signals in the anomeric region, which could arise[4] from the presence of 6,6′-di-*O*-α-D-glucopyranosyl-di-β-D-fructofuranose 1,2′:2,1′-dianhydride (**3**, δ 104.9 for C-2), 6,6′-di-*O*-α-D-glucopyranosyl-di-β-D-fructofuranose 1,2′:2,3′-dianhydride (**4**, δ 104.7 and 98.9 for C-2,2′), and 6-*O*-α-D-glucopyranosyl-α-D-fructofuranose 6-*O*-α-D-glucopyranosyl-β-D-fructofuranose 1,2′:2,3′-dianhydride (**5**, δ 103.5 and 100.8 for C-2,2′) were also found, and this point was further corroborated by chromatographic comparison of the crude reaction mixture with reference samples[4].

After 1 h at room temperature, the intensity of the signals from the side products **3**–**5** had decreased (Fig. 1B). The reaction was then stopped, and the products were simultaneously acetylated, by the addition of a 1:1 mixture of acetic



Scheme 2. Products formed by the action of anhydrous HF on leucrose.

anhydride in pyridine to the HF solution. The usual extraction procedure yielded the crystalline peracetate[4] **2**, which could be readily deacetylated, resulting in compound **1** in two steps from palatinose with an overall yield of 73%.

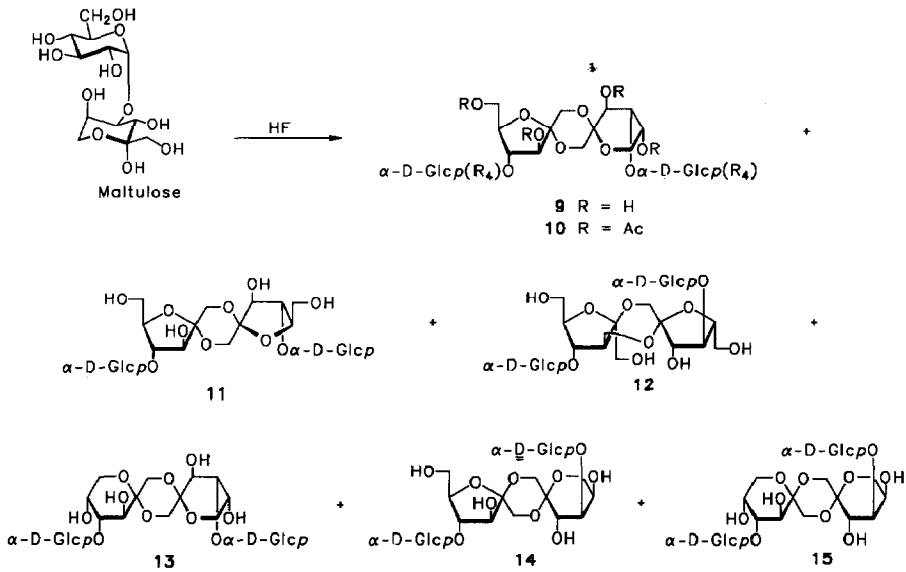
The reaction of leucrose (5-*O*-α-D-glucopyranosyl-D-fructopyranose) in anhydrous HF was slow by comparison with the reaction of palatinose, in that 31% of unreacted material was present in the solution after 5 min, and 15% of the starting sugar was still found after 1 h. This behaviour is in agreement with the expected enhanced reactivity of hexulofuranose species towards protonic reagents. From the ^{13}C NMR spectrum of the crude reaction product, it could be concluded that 5-*O*-α-D-glucopyranosyl-α-D-fructopyranose 5-*O*-α-D-glucopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride (**6**, Scheme 2) was the major component present. Small amounts of 5,5′-di-*O*-α-D-glucopyranosyl-di-β-D-fructopyranose 1,2′:2,1′-dianhydride (**8**) were also suspected[4] from the signal at 97.9 ppm (C-2), and this was confirmed by liquid chromatography (LC). The proportion of **6** did not appreciably change after 1 h (Table I), although the proportion of **8** increased. Taking into account that the separation of **6** from residual leucrose would be easier to achieve than separation from the pseudotetrasaccharide **8**, the reaction was stopped by

TABLE I

Products formed by the action of anhydrous hydrogen fluoride on glycosylfructoses

Glycosylfructose	Reaction products (% of total) at the times indicated	
	5 min [a]	1 h
Palatinose	**1** (75), **3** (18), **4** (3), **5** (3)	**1** (87), **3** (2), **4** (5), **5** (5)
Leucrose	Residual leucrose (31), **6** (66), **8** (3)	Residual leucrose (15), **6** (63), **8** (22)
Maltulose	**9** (59), **11** (18), **12** (12), **13** (9)	**9** (62), **11** (8), **12** (13), **13** (3), **14** (8), **15** (3)
Lactulose	**16** (50), **18** (30), **19** (5)	**16** (69), **18** (11), **19** (5)
Turanose	**20** (61), **22** (26), **23** (13)	**20** (54), **22** (32), **23** (13)

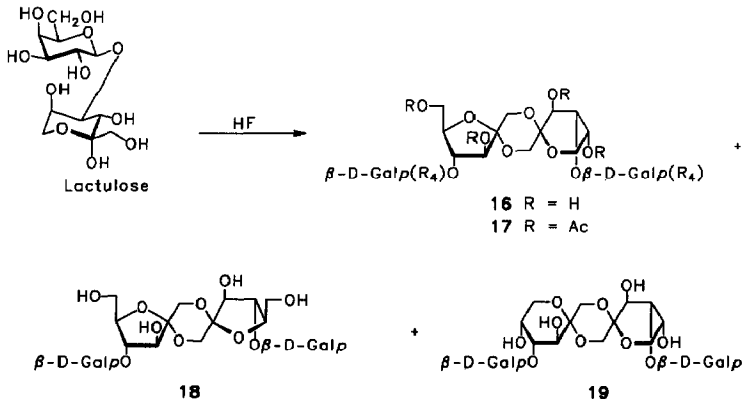
[a] Time required to obtain a homogeneous solution.



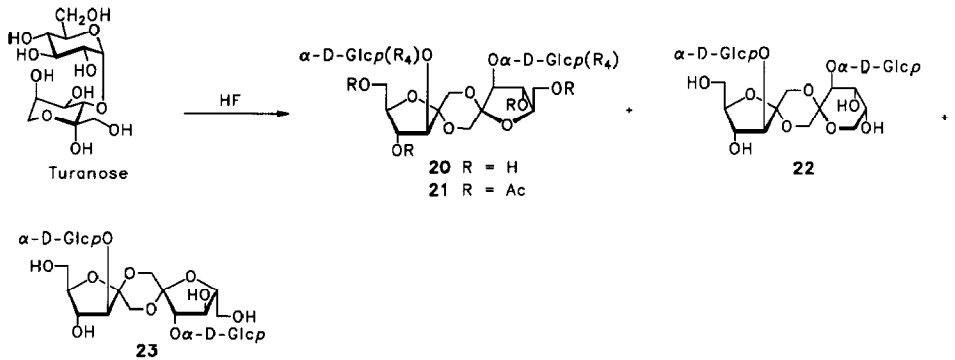
Scheme 3. Products formed by the action of anhydrous HF on maltulose.

pyridine–Ac_2O addition after 5 min. The acetylated derivative **7**, obtained in an overall yield of 61% from leucrose, gave **6** (55% overall) on deacetylation.

Maltulose (4-*O*-α-D-glucopyranosyl-D-fructose) and lactulose (4-*O*-β-D-galactopyranosyl-D-fructose) showed almost the same reactivity as each other when dissolved in anhydrous HF and gave the respective 4,4′-diglycosylated α-D-fructofuranose β-D-fructopyranose 1,2′:2,1′-dianhydrides[4] (**9** and **16**, Schemes 3 and 4), 5 min after dissolution (Table I). Minor isomers were, in both cases, the diglycosylated α,β-difructofuranose 1,2′:2,1′-dianhydrides[4] **11** and **18** (δ 103.6, 100.0, and 103.4, 100.5, respectively, for C-2,2′) and their dipyranose counterparts **13** and **19**



Scheme 4. Products formed by the action of anhydrous HF on lactulose.

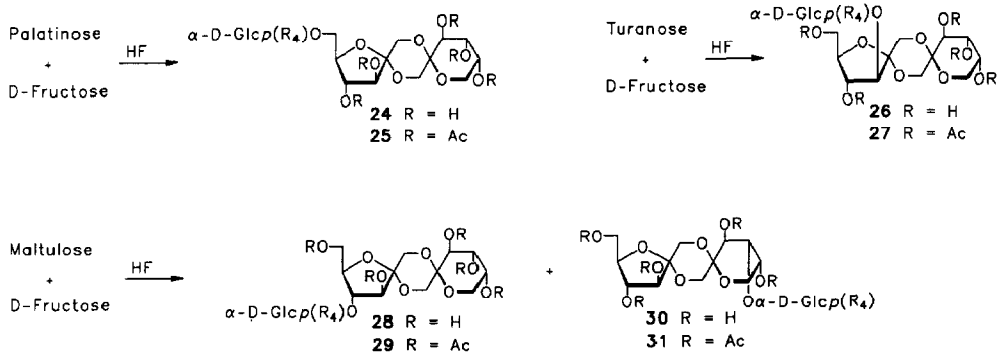


Scheme 5. Products formed by the action of anhydrous HF on turanose.

(δ 95.6, 96.5, and 95.6, 96.3, respectively, for C-2,2′). In addition, the minor diglucosylated difructose dianhydrides **12**, **14**, and **15** were also detected[4] by ^{13}C NMR (δ 104.5, 98.9; 101.7, 97.8, and 98.1, for the respective anomeric carbon atoms) and LC in the product from maltulose after a 1 h reaction time, when the proportion of **9** and **15** together was slightly increased. In situ acetylation of the reaction mixtures after this time allowed, in respective yields of 54 and 61% from maltulose and lactulose, the acetylated diglycosyl difructose dianhydrides **10** and **17** to be obtained, from which **9** and **16** were obtained in 50 and 54% overall yields by deacetylation.

Turanose, (3-*O*-α-D-glucopyranosyl-D-fructose) was almost instantaneously converted into a mixture of three products when dissolved in HF, the diglucosylated α,β-difructofuranose dianhydride (**20**, Scheme 5) being clearly the major component (Table I), with anomeric carbon signals[4] at δ 103.4 and 99.7. Since the relative proportion of products did not change appreciably within 1 h, the HF solution was quenched after 5 min reaction time by addition of the acetylating reagent, resulting in the isolation of the peracetate **21** in 52% yield. Minor products in this reaction were the diglucosylated α-D-fructofuranose β-D-fructopyranose dianhydride **22** and the β,β-difuranose isomer **23** (δ 103.2 and 96.6 for C-2,2′ of **22** and 105.4 for C-2 of **23**, respectively). The overall yield for the 3,3′-diglucosylated α,β-difructofuranose dianhydride **20** from turanose was 49%, following the *O*-deacetylation step.

Noteworthy is that, in all this series of reactions involving dissolution of isomeric glycosylfructoses in anhydrous HF, the D-glycopyranosidic linkage was not at all affected by the highly acidic conditions, although it has been reported[11] that α- and β-hexosides may be cleaved when their solution in HF is kept at temperatures higher than −40°C. It should nevertheless be stressed that dilution is another important parameter to be considered in the reaction, since attempts to run the same synthetic scheme at sugar–HF ratios < 2 resulted in a complex mixture of products in which the original glucosidic linkage was either cleaved or isomerized. Hydrogen fluoride being highly prone to establish hydrogen bonds with hydroxyl-



Scheme 6. Reaction of glycosylfructoses with D-fructose in anhydrous HF.

ated compounds, it should be anticipated that increasing the sugar concentration in this medium would result in a decrease of the protonic availability of the reagent.

The predominant formation of the thermodynamic product in this set of reactions of isomeric glycosylfructoses is a further interesting although anticipated result. As previously noticed[4] from its behaviour in pyridinium poly(hydrogen fluoride), turanose is the only example which does not fit entirely with expectation from stereoelectronic considerations related to the stability of the dispirodioxane system[1,7], since its reaction in HF resulted in the formation of the glucosylated α,β-difructofuranose dianhydride **20** as the major component, a point which is still however in agreement with a tentative explanation already offered[4].

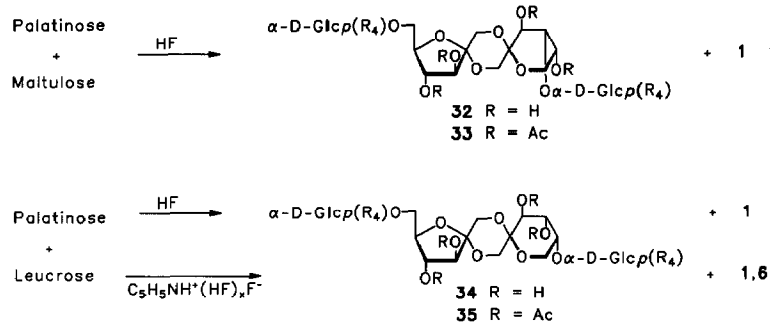
From these considerations it was projected that cross reaction between either two glycosylfructoses, or a glycosylfructose and D-fructose, could be attempted with reasonable chances of success by choosing a suitable stoichiometry of reactants, and this proved to be valid. Thus, when palatinose or turanose was allowed to react with a twofold excess of D-fructose in 2:1 total sugar–anhydrous HF, the expected 6-*O*- and 3-*O*-glucosylated α-D-fructofuranose β-D-fructopyranose 1,2′:2,1′-dianhydrides **24** and **26** were obtained in respective overall yields of 70 and 60% after flash chromatography of the acetylated reaction mixtures containing **25** and **27**, followed by deacetylation (Scheme 6).

The reaction of maltulose and D-fructose under similar experimental conditions resulted in the formation of a ~3:2 mixture of the two isomeric glucosylated α-D-fructofuranose β-D-fructopyranose 1,2′:2,1′-dianhydrides **28** and **30**, which differ in the position of the C-4 glucosyl substituent, which is located at either the fructofuranosyl (**28**) or the fructopyranosyl (**30**) site of the pseudotrisaccharide molecule (Scheme 6). This behaviour is in agreement with the hypothesis which assumes the initial formation of a 4-*O*-glucosyl difructofuranose dianhydride in the kinetic step of the reaction, followed by a rearrangement at one or the other fructose site to give the thermodynamic α-furanose β-pyranose structures **28** and **30**. These were obtained in respective yields of 58 and 37% after purification steps involving the acetylated derivatives **29** and **31**.

TABLE II

^{13}C NMR chemical shifts of the fructose carbon atoms in glucosyl difructose dianhydrides and their peracetates

Compound	^{13}C Chemical shifts (δ)											
	C-2	C-2′	C-3	C-4	C-5	C-3′	C-4′	C-5′	C-6	C-6′	C-1	C-1′
Dianhydrides												
28	103.4	96.5	82.8	84.1	81.3	69.4	69.9	69.9	62.0	62.4	61.7	64.4
30	103.1	96.7	82.8	78.7	84.4	68.9	77.9	69.8	62.1	62.1	62.3	64.4
32	103.4	96.7	82.7	78.8	83.2	68.9	77.8	69.8	67.6	62.3	61.5	64.4
34	103.5	96.6	82.7	78.8	83.3	69.8	70.1	78.8	67.6	62.5	62.0	63.2
Peracetates												
29	101.4	94.9	79.7	83.8	81.9	67.2	68.9	67.4	63.0	61.4	61.2	60.8
31	101.3	94.9	79.4	77.6	80.9	69.0	70.3	69.8	63.0	61.2	61.3	60.8
33	101.3	94.9	80.5	77.7	81.1	69.0	70.3	69.8	67.3	61.2	61.2	60.8
35	102.1	95.0	80.6	77.9	81.4	67.2	69.6	73.8	67.4	62.4	61.5	61.0



Scheme 7. Cross reaction of some glycosylfructoses in anhydrous HF or pyridinium poly(hydrogen fluoride).

Analogously, the 6:4′- and 6:5′-diglucosylated α-D-fructofuranose β-D-fructopyranose 1,2′:2,1′-dianhydrides **32** and **34** were prepared by treatment of 2:1 mixtures of palatinose with maltulose and leucrose, respectively (Scheme 7). In both cases a certain amount of pseudotetrasaccharide **1** was formed by the autocondensation of palatinose, resulting in reduced yields (8.4 and 12.1%, respectively) of **32** and **34**, which were obtained after the usual purification step involving the acetylated derivatives **33** and **35**. An alternative procedure, which used pyridinium poly(hydrogen fluoride) and equimolecular proportions of palatinose and leucrose, resulted in an enhanced yield for **35**, although side products **1** and **6** were together found in the reaction.

Structural confirmations for the previously unknown diglucosyl difructose dianhydrides **28**, **30**, **32**, and **34** were obtained by comparison of the ^{13}C NMR chemical shifts for the carbon atoms of the fructose moieties with those of the parent dianhydride[4,5], taking into account substitution effects in ^{13}C NMR (Table II). Anomeric signals for the dispirodioxanyl part of the molecule (δ 103.1–103.5 and 96.5–96.7) agree well with data[5] for an α-D-fructofuranose β-D-fructopyranose dianhydride substructure. The positive increments (Δδ) observed for C-4 of **28** (4.7), for C-4′ of **30** (8.2), for C-4′ and C-6 of **32** (8.1 and 5.5, respectively), and for C-5′ and C-6 of **34** (8.9 and 5.5 ppm, respectively) as compared to values for the unsubstituted α-furanose β-pyranose dianhydride molecule[4], were in further full agreement with expectations regarding sites of glycosylation.

Recently, hydrogen fluoride has been widely used in the carbohydrate field as a versatile agent for the selective depolymerisation of complex oligo- and poly-saccharides and glycoconjugates[11]. Our present results further support the proposition[12,13] that selective oligosaccharide synthesis can be achieved using this reagent as catalyst.

EXPERIMENTAL

Materials and methods.—Turanose and lactulose were commercial products. Leucrose was kindly provided by Dr. D. Schwengers (Pfeiffer and Langen, Dormagen, Germany) and palatinose by Dr. B. Thiriet (Béghin Say, Paris, France).

Maltulose was prepared by the borate-mediated isomerization of maltose in sodium hydroxide solution[14].

Anhydrous HF was a commercial product obtained in steel cylinders. Prior to use it was distilled and kept in polyethylene bottles at −25°C.

Acetylation was effected conventionally in 1:1 pyridine–Ac_2O (10 mL for 1 g of sample) for isolated products, or by adding the acetylating mixture to the reaction in anhydrous HF (see below). Deacetylation was carried out using the Zemplén technique.

TLC of peracetates was performed on Silica Gel 60 F_{254} plates (E. Merck) and detection was accomplished by charring with H_2SO_4. Flash and column chromatography were performed on Silica Gel 60 (230–400 mesh, E. Merck). Various mixtures of hexane–EtOAc and CCl_4–acetone were used as eluents.

LC of unacylated products was carried out using a Perkin a Elmer 250 pump fitted to a Perkin–Elmer LC-30 refractive index detector. A Lichrosorb RP-18, 5-μm column (250 × 7.5 mm, eluent water) was used under the following conditions: column temperature, 20°C, flow rate, 1.5 mL/min; injection amount, 50 μL of 5% (w/v) sample solution.

^{13}C NMR spectra were recorded with a Bruker AC-200 instrument. Spectra of unacylated products were recorded for solutions in D_2O (internal acetone, 31.1 ppm). For acetylated compounds, solutions in $CDCl_3$ were used with the central peak of the triplet (76.9 ppm) as internal reference. FAB-mass spectra (Cs, acceleration potential 8 kV) were measured in the positive mode with a VG ZAB-SEQ instrument. Glycerol (unacetylated products) and *m*-nitrobenzyl alcohol (peracetylated derivatives) were used as the liquid matrix. NaI was usually added as a cationizing agent.

Microanalyses of unprotected dianhydrides were performed under Ar by the Service Central de Microanalyse du CNRS (Solaize), for samples prepared in sealed tubes after freeze-drying (−65°C, 1.36 Pa, 48 h) and then drying over P_2O_5 under reduced pressure (0.14 Pa, 80°C, 6 h).

General procedures for reactions in anhydrous HF.—All reactions were carried out in capped polyethylene bottles. Hydrogen fluoride was added to the sugar, or intimately ground sugar mixture, in one portion (HF–sugar ratio, ~1:2 v/w), while cooling in a dry ice–acetone bath to avoid initial heating. The mixture was vigorously stirred with a steel spatula and allowed to reach room temperature. A homogeneous stiff solution was obtained within 5 min. The polyethylene bottle was then closed and the mixture was stored at room temperature for the indicated period of time.

For evaluation of the composition of the mixture, ether was added (25 mL for 0.5 mL of HF) and the resulting oily precipitate was washed by decantation with ether (3 × 25 mL). The oil was then triturated with acetone to give an amorphous solid, which was separated again by decantation and dried (P_2O_5). The composition of the product mixtures (Table I) was assessed using two complementary techniques: (*a*) by ^{13}C NMR spectroscopy of solutions in D_2O, using comparative

integration of the intensities of the C-2,2′ resonances of the D-fructose residues, and (*b*) by integration of LC chromatograms obtained under strictly reproducible conditions.

For the preparative scale obtention of glycosyl difructose dianhydrides, 1:1 pyridine–Ac_2O (20 mL for ~ 1 mL of HF solution) was added to the mixture after the chosen period of time, and the resulting solution was kept overnight at room temperature. It was then poured into ice–water (~ 500 mL) and the aqueous solution was made almost neutral by addition of solid $NaHCO_3$, then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with cold H_2SO_4 (M, 3 × 25 mL), satd aq $NaHCO_3$ (2 × 50 mL), and dried (Na_2SO_4). The acetylated material was further processed as described under specific headings below, and then eventually *O*-deacetylated using the Zemplén procedure (NaOMe in MeOH ~ 0.1 M) and freeze-dried.

6-O-α-D-Glucopyranosyl-α-D-fructofuranose 6-O-α-D-glucopyranosyl-β-D-fructofuranose 1,2′:2,1′-dianhydride (**1**).—Starting from palatinose (1 g, 2.9 mmol) and HF (0.5 mL), with 1 h of reaction time followed by pyridine–Ac_2O addition (10 mL), the peracetate **2** was obtained as a syrup which crystallized from EtOH (1.3 g, 79%); mp 187–188°C; $[\alpha]_D^{20}$ + 96° (*c* 0.5, $CHCl_3$); lit.[4] mp 187–188°C, $[\alpha]_D^{20}$ + 96° (*c* 0.5, $CHCl_3$). Deacetylation of **2** gave **1** as a foam (0.67 g, 73% relative to palatinose); $[\alpha]_D^{20}$ + 109° (*c* 0.5, H_2O); lit.[4] $[\alpha]_D^{20}$ + 109° (*c* 0.5, H_2O).

5-O-α-D-Glucopyranosyl-α-D-fructopyranose 5-O-α-D-glucopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride (**6**).—The syrupy product from the reaction of leucrose (1 g, 2.9 mmol) in HF (0.5 mL) for 5 min, followed by acetylation, was submitted to column chromatography (2:3 hexane–EtOAc) yielding the peracetate **7** (1 g, 61%); mp 136–139°C (EtOH); $[\alpha]_D^{20}$ + 72° (*c* 1, $CHCl_3$); lit.[4] mp 136–139°C, $[\alpha]_D^{20}$ + 72° (*c* 1, $CHCl_3$). Deacetylation of **7** gave **6** (0.51 g, 55% relative to leucrose); $[\alpha]_D^{20}$ + 18° (*c* 1, H_2O); lit.[4], $[\alpha]_D^{20}$ + 18° (*c* 1, H_2O).

4-O-α-D-Glucopyranosyl-α-D-fructofuranose 4-O-α-D-glucopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride (**9**).—The syrupy product from the reaction of maltulose (1 g, 2.9 mmol) in HF (0.5 mL) for 1 h, followed by acetylation, was submitted to flash chromatography (2:5 hexane–EtOAc) yielding the peracetate **10** (0.88 g, 54%); mp 119–121°C (EtOH); $[\alpha]_D^{20}$ + 74° (*c* 1, $CHCl_3$); lit.[4] mp 119–121°C, $[\alpha]_D^{20}$ + 74° (*c* 1, $CHCl_3$). Deacetylation of **10** yielded **9** (0.46 g, 50% relative to maltulose); $[\alpha]_D^{20}$ + 89° (*c* 0.8, H_2O); lit.[4] $[\alpha]_D^{20}$ + 89° (c 0.8, H_2O).

4-O-β-D-Galactopyranosyl-α-D-fructofuranose 4-O-β-D-galactopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride (**16**).—The syrupy product from the reaction of lactulose (1 g, 2.9 mmol) in HF (0.5 mL) for 1 h, followed by acetylation, was submitted to flash chromatography (1:2 hexane–EtOAc) yielding the peracetate **17** (0.91 g, 56%); $[\alpha]_D^{20}$ + 28° (*c* 1, $CHCl_3$); lit.[4] $[\alpha]_D$ + 28° (*c* 1, $CHCl_3$). Deacetylation of **17** gave **16** (0.5 g, 54% relative to lactulose); $[\alpha]_D^{20}$ − 14° (*c* 1, H_2O); lit.[4] $[\alpha]_D^{20}$ − 14° (*c* 1, H_2O).

3-O-α-D-Glucopyranosyl-α-D-fructofuranose 3-O-α-D-glucopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride (**20**).—The syrupy product from the reaction of turanose (1 g, 2.9 mmol) in HF (0.5 mL), followed by acetylation, was submitted to

flash chromatography (1:1 hexane–EtOAc) yielding the peracetate **21** (0.85 g, 52%); $[\alpha]_D^{20}$ + 95° (*c* 1, $CHCl_3$); lit.[4] $[\alpha]_D^{20}$ + 95° (*c* 1, $CHCl_3$). Deacetylation of **21** gave **20** (0.45 g, 49% relative to turanose); $[\alpha]_D^{20}$ + 61° (*c* 0.9, H_2O); lit.[4] $[\alpha]_D^{20}$ + 61° (*c* 1, H_2O).

6-O-α-D-Glucopyranosyl-α-D-fructofuranose β-D-fructopyranose 1,2′:2,1′-dianhydride (**24**).—Palatinose (1 g, 2.92 mmol) and D-fructose (1 g, 5.55 mmol) were triturated together in a mortar and treated with HF (1 mL). After 1 h the mixture was cooled (dry ice–acetone) and 1:1 pyridine–Ac_2O (20 mL) was added. The resulting solution was kept overnight at room temperature and then poured into ice–water (1.5 L) to give a white solid (3.1 g), which was filtered, washed with cold water, and dried over P_2O_5. TLC of this crude product (1:1 hexane–EtOAc) showed two main spots with R_f corresponding to di-D-fructose dianhydride hexa-acetates and mono-glucosyl derivatives, respectively, and a faint one for diglucosyl derivatives. Flash chromatography with the above solvent yielded first a fraction (0.6 g) consisting of a mixture of difructose dianhydride hexa-acetates, as seen from a ^{13}C NMR spectrum, and then pure **25** (1.77 g, 70%); $[\alpha]_D^{20}$ + 60° (*c* 1.2, $CHCl_3$); lit.[4] $[\alpha]_D^{20}$ + 60° (*c* 1.2, $CHCl_3$). Deacetylation of **25** gave **24** (0.98 g, 69% relative to palatinose); $[\alpha]_D^{20}$ + 36° (*c* 0.5, H_2O); lit.[4] $[\alpha]_D^{20}$ + 36° (c 0.5, H_2O).

3-O-α-D-Glucopyranosyl-α-D-fructofuranose β-D-fructopyranose 1,2′:2,1′-dianhydride (**26**).—Turanose (1 g, 2.92 mmol) and D-fructose (1 g, 5.55 mmol) were triturated together in a mortar, treated with HF (1 mL), and acetylated as described for **24**. Flash chromatography (1:1 hexane–EtOAc) of the crude product (3 g) gave first a fraction consisting of a mixture of difructose dianhydride hexa-acetates (0.55 g) and then pure **27** (1.51 g, 60%); $[\alpha]_D^{20}$ + 76° (*c* 0.9, $CHCl_3$); lit.[4] $[\alpha]_D^{20}$ + 76° (*c* 0.9, $CHCl_3$). Deacetylation of **27** yielded **26** (0.89 g, 59% relative to the starting turanose); $[\alpha]_D^{20}$ + 51° (*c* 0.8, H_2O); lit.[4] $[\alpha]_D^{20}$ + 51° (*c* 1.2, H_2O).

4-O-α-D-Glucopyranosyl-α-D-fructofuranose β-D-fructopyranose 1,2′:2,1′-dianhydride (**28**) *and α-D-fructofuranose 4-O-α-D-glucopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride* (**30**).—Maltulose (1 g, 2.92 mmol) and D-fructose (1 g, 5.55 mmol) were triturated together in a mortar, treated with HF (1 mL), and acetylated as described for **25**. Flash chromatography (1:1 hexane–EtOAc) of the crude peracetylated product (3.1 g) gave a first fraction consisting of a mixture of difructose dianhydride hexa-acetates (0.65 g) and a second one consisting of a mixture of the peracetates **29** and **31** (1.72 g, 68%). Deacetylation of the second fraction afforded a mixture of trisaccharides **28** and **30** (0.95 g, 67% relative to maltulose). This mixture (200 mg) was subjected to LC to give pure **28** (116 mg, 58%) and **30** (74 mg, 37%) as white solids after freeze-drying.

Compound **28** had: $[\alpha]_D^{20}$ + 61° (*c* 1, H_2O). FABMS: *m/z* 509 (100%, $[M + Na]^+$), 487 (46, $[M + H]^+$). ^{13}C NMR (D_2O): Table II and δ 98.8 (C-1 Glc), 73.6, 73.3, 72.0, 70.3 (C-2 to C-5 Glc), 61.3 (C-6 Glc). Anal. Calcd for $C_{18}H_{30}O_{15}$: C, 44.45; H, 6.22. Found: C, 44.55; H, 6.29.

Compound **30** had: $[\alpha]_D^{20}$ + 48° (*c* 0.8, H_2O). FABMS: *m/z* 509 (100%, $[M + Na]^+$), 487 (60, $[M + H]^+$). ^{13}C NMR (D_2O): Table II and δ 101.3 (C-1 Glc), 73.7,

73.2, 72.6, 70.5 (C-2 to C-5 Glc), 61.5 (C-6 Glc). Anal. Calcd for $C_{18}H_{30}O_{15}$: C, 44.45; H, 6.22. Found: C, 44.49; H, 6.50.

Reacetylation of **28** in 1:1 pyridine–Ac_2O furnished pure syrupy 3,6-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-α-D-fructofuranose 3,4,5-tri-*O*-acetyl-β-D-fructopyranose 1,2′:2,1′-dianhydride (**29**) in quantitative yield; $[\alpha]_D^{20}$ + 40° (*c* 1.2, $CHCl_3$). FABMS: *m/z* 887 (100%, $[M + Na]^+$), 865 (23, $[M + H]^+$). ^{13}C NMR ($CDCl_3$): Table II and δ 95.6 (C-1 Glc), 70.6, 69.6, 68.4, 67.8 (C-2 to C-5 Glc), 61.8 (C-6 Glc). Anal. Calcd for $C_{36}H_{48}O_{24}$: C, 50.00; H, 5.59. Found: C, 50.12; H, 5.51.

Reacetylation of **30** in 1:1 pyridine–Ac_2O gave pure, syrupy 3,4,6-tri-*O*-acetyl-α-D-fructofuranose 3,5-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-fructopyranose 1,2′:2,1′-dianhydride (**31**) in quantitative yield; $[\alpha]_D^{20}$ 0° (*c* 1.0, $CHCl_3$). FABMS: *m/z* 887 (100%, $[M + Na]^+$), 865 (30, $[M + H]^+$). ^{13}C NMR ($CDCl_3$): Table II and δ 95.9 (C-1, Glc), 70.5, 69.2, 68.0, 67.8 (C-2 to C-5 Glc), 61.6 (C-6 Glc). Anal. Calcd for $C_{36}H_{48}O_{24}$: C, 50.00; H, 5.59. Found: C, 50.00; H, 5.30.

6-O-α-D-Glucopyranosyl-α-D-fructofuranose 4-O-α-D-glucopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride (**32**).—Palatinose (2 g, 5.84 mmol) and maltulose (1 g, 2.92 mmol) were triturated together in a mortar, treated with HF (1.5 mL), and acetylated as described for **25**. The resulting peracetylated material (5.2 g) showed two main spots on TLC (3:1 CCl_4–acetone, two successive elutions). Flash chromatography (3.5:1 CCl_4–acetone) afforded **2** (1.5 g) and impure **33** (1.0 g). Further column chromatography using gradient elution with 4:1 → 3:1 CCl_4–acetone afforded pure, syrupy 3,4-di-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-α-D-fructofuranose 3,5-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-fructopyranose 1,2′:2,1′-dianhydride (**33**, 0.3 g, 8.9% relative to maltulose); $[\alpha]_D^{20}$ + 76° (*c* 1, $CHCl_3$). FABMS: *m/z* 1175 (100%, $[M + Na]^+$), 1153 (27, $[M + H]^+$). ^{13}C NMR ($CDCl_3$): Table II and δ 95.9, 95.8 (C-1,1′ Glc), 70.6, 70.5, 69.8, 69.3, 68.1, 67.9 (2C), 67.5 (C-2 to C-5 and C-2′ to C-5′ Glc), 61.5 (2C, C-6,6′ Glc). Anal. Calcd for $C_{48}H_{64}O_{32}$: C, 50.00; H, 5.59. Found: 50.08; H, 5.50.

Deacetylation of **33** (0.3 g) yielded **32** (0.16 g, 8.4% relative to maltulose) as a white solid after freeze-drying; $[\alpha]_D^{20}$ + 91° (*c* 0.8, H_2O). FABMS: *m/z* 671 (100%, $[M + Na]^+$), 649 (33, $[M + H]^+$). ^{13}C NMR (D_2O): Table II and δ 101.3, 99.4 (C-1,1′ Glc), 74.0, 73.7, 73.2, 72.9, 72.6, 72.3, 70.5 (2C) (C-2 to C-5 and C-2′ to C-5′ Glc), 61.5, 61.3 (C-6,6′ Glc). Anal. Calcd for $C_{24}H_{40}O_{20}$: C, 44.45; H, 6.22. Found: C, 44.27; H, 6.17.

6-O-α-D-Glucopyranosyl-α-D-fructofuranose 5-O-α-D-glucopyranosyl-β-D-fructopyranose 1,2′:2,1′-dianhydride. (**34**)—(*a*) The mixture arising from treatment of intimately ground palatinose (2 g, 5.84 mmol) and leucrose (1 g, 2.92 mmol) with HF (1.5 mL), as described for **32**, was acetylated and subjected to column chromatography (successively 4:1, 3.5:1, 3:1 CCl_4–acetone) yielding first **2** (1,7 g) and then 3,4-di-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-α-D-fructofuranose 3,4-di-*O*-acetyl-5-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-

fructopyranose 1,2′ : 2,1′-dianhydride (**35**, 0.43 g, 12.7% relative to leucrose); $[\alpha]_D^{20}$ + 55° (*c* 1, $CHCl_3$). FABMS: *m/z* 1175 (100%, $[M + Na]^+$), 1153 (13, $[M + H]^+$). ^{13}C NMR ($CDCl_3$): Table II and δ 96.4, 96.0 (C-1,1′ Glc), 70.8, 70.6, 70.0, 69.7, 68.7, 68.3, 67.8, 67.7 (C-2 to C-5, C-2′ to C-5′ Glc), 62.0 (2C, C-6, C-6′ Glc). Anal. Calcd for $C_{48}H_{64}O_{32}$: C, 50.00; H, 5.59. Found: C, 49.90; H, 5.19.

Deacetylation of **35** (0.43 g) yielded **34** (0.23 g, 12.1% relative to leucrose), isolated as a white solid after freeze-drying; $[\alpha]_D^{20}$ + 45° (*c* 0.8, H_2O). FABMS: *m/z* 671 (25%, $[M + Na]^+$), 649 (25, $[M + H]^+$). ^{13}C NMR (D_2O): Table II and δ 101.5, 99.5 (C-1,1′ Glc), 74.0, 73.8, 73.1, 73.0, 72.8, 72.3, 70.4, 70.3 (C-2 to C-5 and C-2′ to C-5′ Glc), 61.6, 61.5 (C-6,6′ Glc). Anal. Calcd for $C_{24}H_{40}O_{20}$: C, 44.45; H, 6.22. Found: C, 44.71; H, 6.26.

(*b*) Palatinose (0.5 g, 1.46 mmol) and leucrose (0.5 g, 1.46 mmol) were triturated together in a mortar and treated with pyridinium poly(hydrogen fluoride) (pyridine–HF ratio 7 : 3 v/v, 2 mL) at 0°C with magnetic stirring, as described in ref 4. The mixture was stored at 20°C for 30 min, quenched (liquid N_2), and ether (4 × 20 mL) was added and decanted after vigorous stirring. The oily residue was triturated with acetone (20 mL) to give a solid, which was separated by decantation, dried over P_2O_5, and acetylated. A TLC (3 : 1 CCl_4–acetone, two elutions) of the crude peracetylated material showed three spots. Column chromatography (4 : 1, then 3,5 : 1, then 3 : 1 CCl_4–acetone) yielded successively **2** (0.27 g), **35** (0.36 g, 21.3%), and **7** (0.14 g). Deacetylation of **35** yielded **34** (0.20 g, 20.1%).

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REFERENCES

1 J. Defaye and J.M. García Fernández, *Tetrahedron Lett.*, 33 (1992) 7861–7864.
2 T. Uchiyama, K. Tanaka, and M. Kawamura, *J. Jpn. Soc. Starch Sci.*, 35 (1988) 113–120.
3 M. Tanaka, K. Nishio, and H. Hashimoto, *Int. Carbohydr. Symp. 15th*, 1990, *Abstr.*, C059, p 361.
4 J. Defaye and J.M. García Fernández, *Carbohydr. Res.*, 237 (1992) 223–247.
5 J. Defaye, A. Gadelle, and C. Pedersen, *Carbohydr. Res.*, 136 (1985) 53–65.
6 J. Defaye, A. Gadelle, and C. Pedersen, *Carbohydr. Res.*, 152 (1986) 89–98.
7 K. Bock, C. Pedersen, J. Defaye, and A. Gadelle, *Carbohydr. Res.*, 216 (1991) 141–148.
8 A. Bouchu, J. Chedin, J. Defaye, D. Lafont, and E. Wong, Fr. Demande FR, 2, 599, 040 (1987); *Chem. Abstr.*, 109 (1988) 95053a; Wo. Pat., 87, 07, 275 (1987).
9 J. Defaye and J.M. García Fernández, Fr. Demande, FR 91, 10818 (1991).
10 J. Defaye and J.M. García Fernández, *Carbohydr. Res.*, (A-602).

11 Yu.A. Knirel, E.V. Vinogradov, and A.J. Mort, *Adv. Carbohydr. Chem. Biochem.*, 47 (1989) 167–202.
12 For a review, see J. Defaye and C. Pedersen, *Zuckerindustrie (Berlin)*, 116 (1991) 271–276.
13 J. Defaye, A. Gadelle, and C. Pedersen, *Carbohydr. Res.*, 186 (1989) 177–188.
14 K.B. Hicks, E.V. Symanski, and P.E. Pfeffer, *Carbohydr. Res.*, 112 (1983) 37–50.