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Convenient access to 4-O-glycosylated 1,5-anhydro-D-fructoses via disaccharide-derived 2-hydroxyglycal esters ☆

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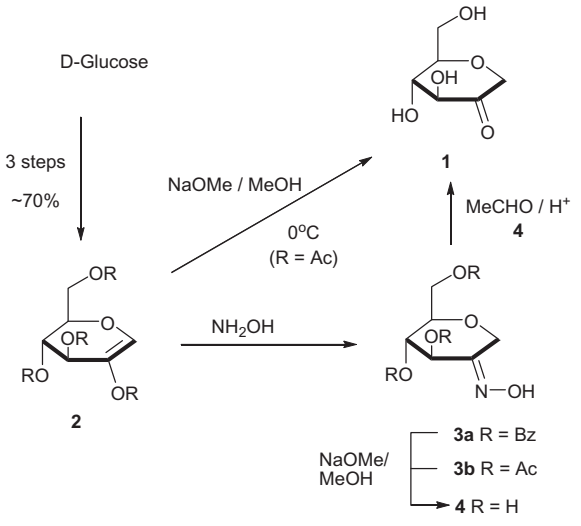
ABSTRACT

Efficient six-step protocols are described for the conversion of common disaccharides, such as maltose, cellobiose, or lactose, into the corresponding 4-*O*-glycosyl-1,5-anhydro-D-fructoses. Overall yields of 40–45% are favorably compared to the alternative eleven-step procedure from their monosaccharide components (~15%).

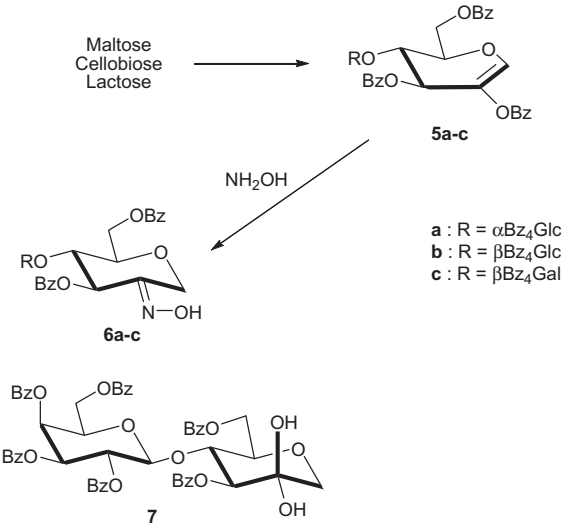
1. Introduction

Thirty years ago, and seven years before being encountered as a naturally occurring monosaccharide,[2] 1,5-anhydro-D-fructose **1** was synthesized from D-glucose in a six-step sequence,[3] the first three steps comprising of the generation of its 2-hydroxyglucalester **2**,[4] the others being the selective hydroxylaminolysis[5] of the enol ester group **2**→**3**, Zemplén de-O-acylation, and deoximation (**3**→**4**→**1**) (Scheme 1). Since then, various other enzymatic[6] and chemical[7] approaches to 1,5-anhydro-D-fructose, usually characterized as the monohydrate, have been developed, among them the direct low-temperature deacetylation of the acetylated hydroxyglucal ester **2** (R = Ac).[3b,7b]

Either of these simple approaches to 1,5-*anhydro*-D-fructose, should in principle be applicable to any of the common disaccharides, a conjecture which has already been verified[8] by conversion of maltose, cellobiose, and lactose, via their 2-hydroxyglycal esters **5a**–**5c** into the respective perbenzoylated 4-*O*-glycosyl-1,5-anhydrofructoses **6a**–**6c**, with yields in the 70% range for the four steps involved[8] (Scheme 2). The lactose-derived **6c** was even deoximated to the respective, highly crystalline ulose monohydrate **7**.[8]



Scheme 1. Chemical approaches to 1,5-anhydro-D-fructose.



Scheme 2. Disaccharide-derived 1,5-anhydrofructose derivatives.[8]

☆ Part 45 of the series, Sugar-Derived Building Blocks'; for Part 44, see Ref. 1.

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Apparently unaware of this expedient, large scale adaptable access to 4-O-glycosylated 1,5-anhydrofructoses, recently, Agoston et al. patented[7b] and published[9] another approach comprising of the glycosylation of a bicyclic 1,5-anhydrofructose derivative with glycosyl trichloracetimidates, an inconvenient route due to the 11 steps required, three for the donor subtrate;[10] five for the acceptor;[7c] and another three for the targets[9] with overall yields of around 15%.

Due to potential medical applications,[11] interest in 1,5-anhydro-D-fructose has substantially increased recently, an appeal that extends to its glycosylated analogues, in as much as a α(1→3)-1,5-anhydrofructose prepared by enzymatic transglucosylation was deemed suitable for conjugation with proteins[12] and as antioxidant food additives.[13] Since their generation via 2-hydroxyglucal esters from the common disaccharides was considered to be significantly more simple than glycosylations of 1,5-anhydrofructose derivatives, we have resumed our earlier work[8] and herein describe the straightforward deprotection of the 4-*O*-glycosyl-1,5-anhydrofructose oximes **6a**–**6e** to the underlying free disaccharides.

2. Results and discussion

In view of the most expedient access to 1,5-anhydro-D-fructose via de-O-acetylation of 2-acetoxy-D-glucal triacetate **2**→**1**,[3b,7b] it appeared obvious to generate glycosylated analogues of **1** from disaccharide-derived 2-hydroxyglucal esters. When applied to the maltal- and cellobial-derived **5d** and **5e**, the reaction produced several products in addition to the desired 4-*O*-glucosyl-1,5-anhydrofructoses **9f** and **9g**; among them, substantial amounts of D-glucose, obviously originating from base induced β-elimination, a reaction readily occurring with 2-hydroxyglycal esters under mild basic conditions.[3,5] As chromatographic purification proved quite laborious, this access was not elaborated.

In the case of disaccharides carrying the glycosyl residue at positions other than *O*-4, however, such as the (1→6)-intersaccharidic isomaltose, gentiobiose, or melibiose, the low-temperature deacytelation procedure may well be used to efficiently generate 1,5-anhydrofructoses with α-D-glucosyl-, β-D-glucosyl or β-D-galactosyl residues at *O*-6.

Application of the three-step sequence hydroxylaminolysis, de-O-acylation and deoximation to any of the disaccharide-derived 2-hydroxyglucal esters **5a**–**5e** proceeded in a preparatively straightforward manner. The established hydroxylaminolysis protocol,[5,8] 3,5-4 molar hydroxylamine hydrochloride in pyridine at ambient temperature (24 h) or at 70 °C (4 h), smoothly afforded the glycosyl-(1→4)-1,5-anhydrofructose *E*-oximes **6a**–**6e** isolable in excellent yields of 85–90%.

That these products invariably have their N–OH group oriented toward the less congested, proanomeric center, that is, are *E*-oximes as indicated in the formulae, follows, among other indications, from the chemical shift for their equatorial H-1, which appears within the same narrow range as in the acylated 1,5-anhydrofructoses **3a** and **3b** (Table 1), that is, show the same significant downfield shift caused by the nearly coplanar N–OH group as seen.[1,14]

The release of the free glycosyl-(1→4)-1,5-anhydrofructoses **9f**–**9h** from their oximes proceeded in the expected manner: de-O-acylation under Zemplén conditions (NaOMe/MeOH, rt, 12–24 h) smoothly afforded the respective oximes **8f**–**8h**, each isolated and characterized as *E*/*Z*-mixtures, since the basic conditions obviously induced *E*→*Z* equilibrations. The *E*-isomers thereby constituted the main components in up to 5:1 preference, yet none crystallized as was the case with the monosaccharidic 1,5-anhydro-D-fructose *E*-oximes **4**.[3] Although separable by chromatography due to the sufficiently different R_f values, the *E*/*Z*-oxime mixtures **8f**–**8h** were directly subjected to transoximation by exposure, in an acetonitrile solution, to excess acetaldehyde in the presence of 1 M HCl (6 h, rt). The resulting glycosyl-(1→4)-1,5-anhydrofructoses **9f**–**9h** (Scheme 3) were secured in the form of glasses or fluffy solids by freeze-drying their Sephadex-purified aqueous solutions, with yields being in the 75% range only, due to the somewhat elaborate purification procedure. Analytical values were uniformly within the acceptable limits for the monohydrate ($C_{12}H_{20}O_{10}\cdot H_2O$) or 2,2-dihydroxy forms, as indicated in the formulae. Unequivocal structural proof followed from their ^1H and ^{13}C NMR spectra of **9f**–**9h** in D_2O (pertinent data shown in Table 2) which conclusively revealed the signal and coupling patterns expected for their 4-*O*-glycosyl and 1,5-anhydrofructose portions.

Moreover, our NMR data for the glycosyl-β(1→4)-1,5-anhydrofructose **9g** and **9h** corresponded well with those obtained for **9g** and **9f** prepared via glycosylation of a 4-OH-free 1,5-anhydrofructose derivative,[9] albeit there are minor shift differences. The microanalytical data, however, are distinctly different. While our glycosyl-1,5-anhydrofructoses **9f**–**9h** invariably give satisfactory C, H values for the monohydrate or 2,2-dihydroxy forms, the respective Agoston et al.[9] products represent dihydrates, as evidenced by essentially perfect analytical values for $C_{12}H_{20}O_{10}\cdot 2H_2O$ (or $C_{12}H_{22}O_{11}\cdot H_2O$ in their notation), thereby fostering reservations as to the integrity of these products. Similar reservations also apply to two 4-*O*-glycosyl-1,5-anhydro-tagatoses prepared in the same way.[9] They analyze for monohydrates, whereas 1,5-anhydro-D-tagatose exhibits a pronounced tendency to adapt the 2-carbonyl form in aqueous solution and in the solid state.[6d,14] A clarification of these inconsistencies appears to be de rigueur.

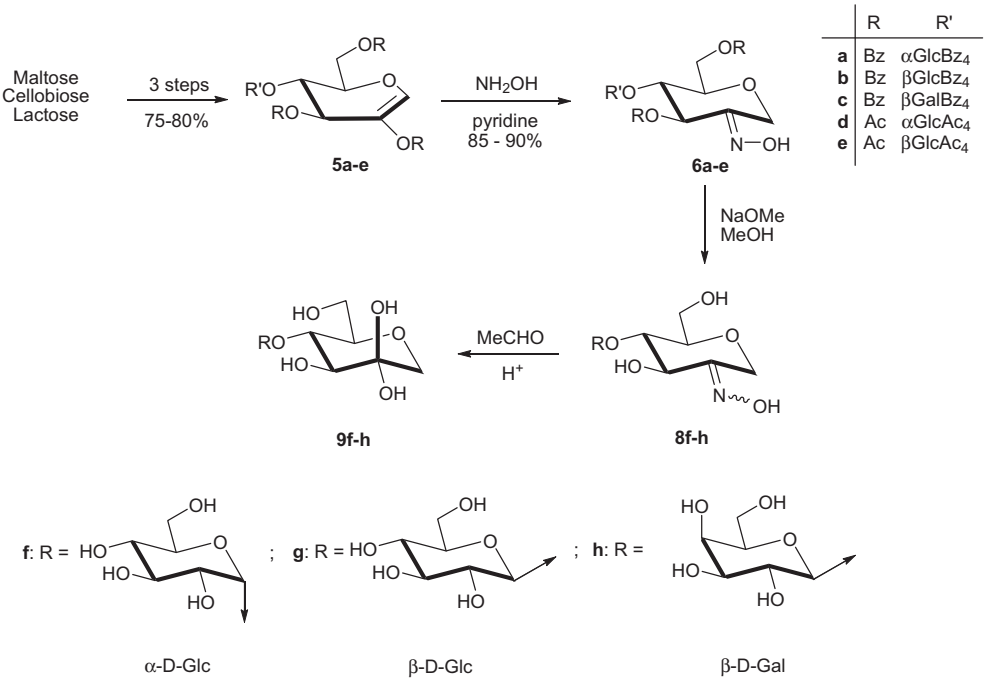
3. Conclusion

Efficient, large scale-adaptable protocols are presented for the conversion of common bulk disaccharides such as maltose, cellobiose, or lactose via their 2-hydroxyglycal esters into the respective glycosyl-(1→4)-1,5-anhydrofructoses. The yields attainable are in the 40–45% range for the six steps involved, which compares favorably with the 15% yield over the eleven step procedure,[9] when acquiring these products from glucose and fructose, respectively.

Table 1
Pertinent ^1H NMR data (500 MHz) for acylated 1,5-anhydro-D-fructose *E*-oximes and its 4-*O*-glycosyl analogs

Compound	R[a]	R′	Solvent	H-1e	H-1a	H-3	H-4	NOH	H-1′	$J_{1,1}$	$J_{3,4}$	$J_{4,5}$	$J_{1',2'}$	Ref.
3a	Bz	Bz	DMSO-d_6	5.13	4.28	6.13	5.63	11.35	—	14.8	8.4	8.8	—	
			$CDCl_3$	5.17	4.22	6.02	5.72	8.55	—	15.8	7.2	8.1	—	3b
6a[b]	αGlcBz$_4$	Bz	$CDCl_3$	4.92	4.48	5.91	5.45	8.29	5.62	16.7	3.8	10.3	3.9	
6b[b]	βGlcBz$_4$	Bz	$CDCl_3$	4.83	4.23	6.03	4.20	8.54	5.11	16.5	4.0	8.2	8.0	
6c[b]	βGalBz$_4$	Bz	$CDCl_3$	4.98	4.32	6.18	4.36	8.40	5.18	16.4	4.5	8.1	8.0	
3b	Ac	Ac	DMSO-d_6	4.88	4.04	5.54	4.94	11.48	—	15.0	8.0	8.9	—	3b
6d	αGlcAc$_4$	Ac	$CDCl_3$	4.85	4.20	5.27	3.85	8.23	5.14	16.5	4.5	7.7	4.0	
6e	βGlcAc$_4$	Ac	$CDCl_3$	4.90	4.26	5.73	4.97	8.71	4.70	16.4	4.4	9.5	8.1	

[a] Abbreviations as in Scheme 3.
[b] Previously,[8] only 100 MHz data were given.



Scheme 3. Six-step conversion of common disaccharides into 4-*O*-glycosyl-1,5-anhydrofructoses.

Table 2
Significant ^{1}H and ^{13}C NMR data (500 resp. 75,5 MHz in D_2O) for the monohydrates of 1,5-anhydro-D-fructose and its 4-*O*-glycosyl derivatives **9f**–**9h**

Signals	**1**[3b]	**9f**	**9g**	**9h**
H-1e	3.76	3.69	3.70	3.59
H-1a	3.46	3.42	3.41	3.30
H-3	3.56	3.50	3.60	~3.50
H-4	3.44	3.48	[a]	[a]
H-1′	–	5.26	4.40	4.35
$J_{1,1}$	12.1	12.4	12.1	12.0
$J_{3,4}$	8.9	8.1	[a]	[a]
$J_{4,5}$	10.1	8.5	[a]	[a]
$J_{1',2'}$	–	3.8	7.9	7.8
C-1	73.3	73.0	71.8	72.0
C-2	93.9	93.5	93.1	93.2
C-3	78.4	78.9	79.3	79.0
C-4	70.4	78.7	79.7	79.4
C-5	82.2	81.5	75.7	75.9
C-6	62.0	63.0	61.1	61.5
C-1′	–	99.7	103.0	103.7

[a] Not unequivocably assignable due to complex overlap of multiplets.

4. Experimental

4.1. General

Melting points were determined with a Bock hot-stage microscope and are uncorrected. Optical rotations were measured at 20 °C with a Perkin-Elmer 241 polarimeter using a cell of 1 dm path length. ^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX 300 and Avance 500 instruments. Mass spectra were acquired on Varian MAT 311 spectrometer, microanalyses on a Perkin-Elmer 240 elemental analyzer. Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F_{254} plastic sheets (Merck, Darmstadt) with detection by UV light or by spraying with 50% sulfuric acid and charring at 140 °C for 5 min. Column chromatography was performed on Silica Gel 60 (Merck, 63–200 ppm) using the specified eluents.

4.2. 3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-1,5-anhydro-D-fructose *E*-oxime 6d

To a solution of $NH_2OH{\cdot}HCl$ (2.4 g, 35 mmol) in pyridine (100 mL) were added 6.2 g (10 mmol) of 2-acetoxymaltal hexaacetate **5d**[15] and the mixture was stirred at ambient temperature until the educt had disappeared (ca. 24 h, $R_f = 0.33 \rightarrow 0.21$ in 2:1 toluene–EtOAc). Most of the solvent was removed by evaporation in vacuo (40 °C bath temperature) and the residue was dissolved in a mixture of water and $CHCl_3$ (150 mL each), followed by separation and extraction of the water layer with $CHCl_3$ (2×100 mL). The combined $CHCl_3$ extracts were washed with ice-cold 1 M HCl solution and water, dried ($MgSO_4$), and taken to dryness in vacuo. The sirupy residue crystallized on trituration with EtOH: 4.75 g (81%) of **6d** as colorless needles (2 crops); mp 168–170 °C; $[\alpha]_D^{20} = -61.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.95–2.03 (six 3H-s, 6 OAc), 3.58 (ddd, 1H, H-5), 3.85 (dd, 1H, H-4), 3.96 (ddd, 1H, H-5′), 4.01 and 4.17 (two 1H-dd, 6-H_2), 4.11 and 4.31 (two dd, 6′-H_2), 4.20 (1H-d, H-1α), 4.81 (1H-dd, H-2′), 4.85 (1H-dd, H-1β), 4.98 (1H-dd, H-4′), 5.27 (1H-d, H-3), 5.31 (1H-dd, H-3′), 5.41 (1H-d, H-1′), 8.23 (1H-s, NOH); $J_{1,1} = 16.5$, $J_{3,4} = 4.5$, $J_{4,5} = 7.7$, $J_{5,6} = 2.3$ and 4.5, $J_{6,6} = 12.4$; $J_{1',2'} = 4.0$, $J_{2',3'} = 10.4$, $J_{3',4'} = J_{4',5'} = 9.6$, $J_{5',6'} = 2.7$ and 6.3, $J_{6',6'} = 12.1$ Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.9–21.2 (6 AcCH_3), 62.1 and 64.1 (C-6, C-6′), 63.1 (C-1), 68.6–70.4 (C-5, C-2′–C-4′), 72.1 (C-3), 75.4 and 77.1 (C-4, C4′), 95.8 (C-1′), 151.9 (C-2). Anal. Calcd for $C_{24}H_{33}NO_{16}$ (591.51): C, 48.73; H, 5.62; N, 2.37. Found: C, 48.61; H, 5.57; N, 2.29.

4.3. 3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,5-anhydro-D-fructose *E*-oxime 6e

Hydroxylaminolysis of 2-acetoxy-cellobial hexaacetate **5a**[16] (10.2 g, 16.4 mmol) was effected by stirring in pyridine (100 mL) containing $NH_2{\cdot}HCl$ (10.0 g, 0.15 mol) for about 24 h at room temperature ($R_f = 0.27 \rightarrow 0.16$ in 2:1 toluene–EtOAc). Work-up as described above for **6d** gave a sirupy residue crystallizing from

EtOH: 8.24 g (85%) of **6e** in two crops; colorless needles of mp 159–161 °C; $[\alpha]_D^{20} = -25.9$ (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 2.00–2.10 (six 3H-s, 6 Ac-CH_3), 3.51 (1H-ddd, H-5), 3.78 (1H-ddd, H-5′), 3.83 (1H-dd, H-4), 4.09 and 4.11 (two 1H-dd, H-6a and H-6b), 4.26 (1H-d, H-1α), 4.30 and 4.31 (two 1H-dd, H-6b and H-6b′), 4.70 (1H-d, H-1′), 4.90 (1H-d, H-1β), 4.97 (1H-dd, H-2′), 5.08 (1H-t, H-3′), 5.19 (1H-t, H-4), 5.73 (1H-d, H-3), 8.71 (1H-s, NOH); $J_{1,1} = 16.4$, $J_{3,4} = 4.4$, $J_{4,5} = 8.1$, $J_{5,6} = 2.6$ and 4.9, $J_{6,6} = 11.9$, $J_{1',2'} = 8.1$, $J_{2',3'} = J_{3',4'} = J_{4',5'} = 9.5$, $J_{5',6'} = 4.9$ and 6.1, $J_{6',6'} = 12.0$ Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.5–20.7 (AcCH_3), 61.8, 63.1 and 63.4 (C-1, C-6, C-6′), 71.0, 71.4, 72.1, 72.8 (C-3, C-2′, C-3′, C-5′), 76.5 (C-5), 79.0 (C-4), 101.4 (C-1′), 151.5 (C-2). Anal. Calcd for $C_{24}H_{33}NO_{16}$ (591.51): C, 48.73; H, 5.62; N, 2.37. Found: C, 48.69; H, 5.51; N, 2.30.

4.4. 4-*O*-(α-D-Glucopyranosyl)-1,5-anhydro-D-fructose *E*/*Z*-oxime 8f

Commercial 30% methanolic sodium methoxide (1.3 mL) was added with stirring to a solution of maltose-derived oxime hexaacetate **6d** (3.75 g, 6.3 mmol) in methanol (150 mL) TLC monitoring after about 2 h with 8:5:1 *i*PrOH/EtOAc/water showed complete conversion of the educt into an approximate 2.5:1 mixture of *E*/*Z*-isomers (^1H NMR) of $R_f = 0.54$ (tentatively the *E*-isomer) and 0.27, respectively. The solution was then deionized by briefly stirring with Amberlite 120 (H^+ form) filtration and washing of the resin with methanol. The filtrate and washings were subjected to a brief charcoal treatment followed by an in vacuo removal of the solvent, finally at 0.1 Torr: 1.78 g (83%) of *E*/*Z*-**8f** as a fluffy solid. ^1H NMR (500 MHz, D_2O): 5.20 (1H-d, $J_{1',2'} = 3.8$ Hz, H-1′), 5.12 (1H-d, $J_{3,4} = 3.8$ Hz, H-3), 4.90 and 4.20 (two 1H-d, $J_{1,1} = 16.1$ Hz, 1-Hβ, and 1-Hα) for the major, conceivably the *E*-isomer; other signals not interpreted due to *E*/*Z*-mixture and extensive overlap. Anal. Calcd for $C_{12}H_{21}NO_{10}$ (339.29): C, 42.48; H, 6.24; N, 4.13. Found: C, 42.29; H, 6.17; N, 4.06.

The *E*/*Z*-isomeric oximes, due to sufficiently different mobilities ($R_f = 0.54$ and 0.27, resp.), may be separated by chromatography on a silica column, yet the pure isomers tend to equilibrate upon removal of the elution solvents. Thus, the *E*/*Z*-mixture was subjected directly to deoximation (→**9f**, see below).

4.5. 4-*O*-(α-D-Glucopyranosyl)-1,5-anhydro-D-fructose monohydrate 9f

Acetaldehyde (0.57 mL, 10 mmol) and 1 M HCl (5 mL) was added to a suspension of the *E*/*Z*-oxime mixture **8f** (1.20 g, 3.5 mmol) in acetonitrile (25 mL), followed by stirring at ambient temperature for 5 h. Dilution with water (10 mL), neutralization by briefly stirring with a basic resin, in vacuo evaporation to a small volume (~2 mL), elution from an LH 20 Sephadex column (25 × 2 cm) with water, and lyophilization of the product-carrying eluates gave the disaccharide monohydrate **9f** as a colorless foam (630 mg, 74%). ^1H NMR (500 MHz, D_2O, 5 h after solution for equilibration): δ 5.29 (1H-d, $J_{1',2'} = 3.8$ Hz, H-1′), 3.80 and 3.68 (two 2H-m, 6-H_2, 6′-H_2, 3.71 and 3.42 (two 1H-d, $J_{1,1} = 12.4$ Hz, H-1β, and H1α), ~3.60 (br m, H-4, H-5, H-2′, H-3′), 3.50 (14-d, $J_{3,4} = 8.1$ Hz, H-3), 3.35 (1H-m, H-4′). ^{13}C NMR (75.5 MHz, D_2O): δ 99.7 (C-1′), 80.1 (C-5), 78.9 and 78.7 (C-3, C-4), 73.6 (C-3′), 73.0 (C-1), 72.4 and 72.2 (C-2, C-5′), 70.1 (C-4′), 61.8 and 61.3 (C-6, C-6′). Anal. Calcd for $C_{12}H_{20}O_{10}{\cdot}H_2O$ (342.30): C, 42.10; H, 6.48. Found: C, 41.82; H, 6.39.

De-O-benzoylation of maltose-derived oxime hexabenzoate **6a** (→**8a**) and subsequent deoximation with acetaldehyde in a procedure identical to the galactosyl analogue **6c** (see Section 4.7) afforded **9f** in 66% yield.

4.6. 4-*O*-(β-D-Glucopyranosyl)-1,5-anhydro-D-fructose monohydrate 9g

To a stirred solution of cellobiose-derived oxime hexaacetate **6e** (4.15 g, 7.0 mmol) in dry methanol (200 mL) was added 2.0 mL of a commercial 30% (5.56 M) methanolic sodium methoxide solution and the mixture was stirred at ambient temperature. After about 3 h, (TLC monitoring in 5:3:1 *i*-PrOH/EtOAc/water revealed products at $R_f = 0.62$ and 0.71) the solution was deionized with a small amount of Amberlite IR 120 (H^+ form) and, subsequently, subjected to charcoal treatment. Removal of the solvent in vacuo gave the sirupy **8g** (2.1 g, 88%) as an approximate 3:1 mixture (^1H NMR) of *E*/*Z*-isomers. (major) 3.8 Hz-d for H-3 at 5.16, 15.5 Hz-d for H-1β at 4.95 ppm; minor: H-3 as 3.4 Hz-d at 5.02, H-1β as 15.9 Hz-d at 4.93 ppm).

Deoximation of the *E*/*Z*-mixture **8g** (2.0 g, 5.9 mmol) was effected by stirring in acetonitrile (40 mL) with acetaldehyde (1 mL, 17.5 mmol) and M HCl (8 mL) at rt for 5 h, followed by dilution with water (15 mL) neutralization by briefly stirring with a basic resin, and in vacuo evaporation to give a sirup. Purification by elution from a silica gel column (2 × 20 cm) with 7:3 *n*-propanol–water and in vacuo evaporation of the product-carrying eluates gave 1.27 g (63 %) of **9g** as a fluffy solid. $[\alpha]_D^{20} = -21.2$ (*c* 1.0, water); ^1H NMR (500 MHz, D_2O, 3 h after dissolution): δ 4.40 (1H-d, $J_{1',2'} = 7.9$ Hz, H-1′), 3.90 and 3.75 (two 2H-m, 6-H_2, 6′-H_2), 3.70 and 3.42 (two 1H-d, $J_{1,1} = 12.1$ Hz, H-1β and H-1α), 3.60 (2H-m, H-3, H-4), 3.40 (br 4H-m, H-5, H-3′–H-5′), 3.26 (1H-m, H-2′). ^{13}C NMR (D_2O): δ 103.0 (C-1′), 93.1 (C-2), 79.7 and 79.4 (C-3, C-4), 76.2 (C-3, C-5′), 75.7 (C-5), 74.0 (C-2′), 71.8 (C-1), 70.3 (C-4′), 60.9 (C-6, C-6′). Anal. Calcd for $C_{12}H_{20}O_{10}{\cdot}H_2O$ (342.30): C, 42.10; H, 6.48. Found: C, 42.02; H, 6.50.

Whilst these ^1H and ^{13}C NMR data correspond fairly well with those reported by Agoston et al.[9] (there were some minor chemical shift differences) their microanalytical data (found:[9] C, 40.09; H, 6.65) do not, as these are distinctly too low; however, they match those required for $C_{12}H_{22}O_{10}.H_2O$ (sum formula given in Ref. 9), which factually is a dihydrate (calcd for $C_{12}H_{18}O_9{\cdot}2H_2O$: C, 40.00; H, 4.71). These peculiar incongruities remain to be clarified.

De-O-benzoylation of oxime hexabenzoate **6b**, directly followed by deoximation in a procedure as detailed for the galactosyl analogue (see Section 4.7) afforded **9f** in 61% yield.

4.7. 4-*O*-(β-D-Galactopyranosyl)-1,5-anhydro-D-fructose monohydrate 9h

Lactose-derived oxime hexabenzoate **6c** (2.40 g, 2.5 mmol) was stirred in 30 mL of a 0.1 M methanolic NaOMe solution (prepared by adding 5.4 mL of commercial NaOMe/MeOH to 25 mL of MeOH) resulting in a clear solution after about 30 min. Stirring was continued for another 3 h (TLC monitoring), and the solution was diluted with 100 mL of MeOH, and neutralized by stirring with Dowex 50 WX8, H^+ form, for 10 min. Filtration, washing of the resin with MeOH, and in vacuo evaporation of the filtrate and washings gave a sirup, comprising an approximate 3:2 *E*/*Z*-oximes **8h** (740 mg, 87%); ^1H NMR in D_2O: H-3as 3.8 Hz-d at 5.10 ppm for the major and 3.3 Hz-d at 4.94 for the minor isomer.

The product was directly subjected to deoximation with acetaldehyde (0.5 mL) in acetonitrile (20 mL) and 4 mL of M HCl (5 h, rt), followed by dilution with water (10 mL), neutralization with a basic resin and in vacuo evaporation to a sirup. Purification by elution from a silica gel column (2 × 20 cm) with 7:3 *n*-PrOH/water and in vacuo evaporation of the product-carrying fractions left 570 mg of **9h** (67%, based on **6c**) as a glass; $[\alpha]_D^{25} = -22.3$ (*c* 0.8, water); ^1H NMR (500 MHz, D_2O): δ 4.35 (d, 1H, $J_{1',2'} = 7.9$ Hz, H-1′), 3.78–3.62 (complex m, 6-H_2, 6′-H_2, H-5, H-5′), 3.59 and 3.30 (two 1H-d, $J_{1,1} = 12.0$ Hz, H-1β and H-1α), ~3.50 (3H-m, H-3, H-3′, H-4′),

~3.40 (2H-m, H-4, H-2′). ^{13}C NMR (75.5 MHz, D_2O): δ 103.7 (C-1′), 93.2 (C-2), 79.4 (C-4), 79.0 (C-3), 75.9 (C-5, C-5′), 73.1 (C-3′), 72.0 (C-1), 71.4 (C-2′), 69.2 (C-4′), 61.5 and 61.2 (C-6, C-6′). Anal. Calcd for $C_{12}H_{20}O_{10}\cdot H_2O$ (342.30): C, 42.10; H, 6.48. Found: C, 41.98; H, 6.40.

The NMR data reported by Agoston et al.[9] for **9h** corresponded reasonably well to those described above, yet their microanalytical data (found:[9] C, 39.94; H, 6.72) are too low by an intolerable 5%. Curiously, they correspond perfectly to $C_{12}H_{22}O_{10}\cdot H_2O$,[9] which de facto is a dihydrate $C_{12}H_{20}O_9\cdot 2H_2O$ (calcd C, 40.00; H, 6.71).

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