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

Toshio Nakagawa, Frieder W. Lichtenthaler
Clemens-Schöpf-Institut für Organische Chemie und Biochemie, Technische Universität Darmstadt, Petersenstraße 22, D-64287 Darmstadt, Germany

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%).

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1. Introduction

Thirty years ago, and seven years before being encountered as a naturally occurring monosaccharide, 1,5-anhydro-D-fructose 1 was synthesized from D-glucose in a six-step sequence, the first three steps comprising of the generation of its 2-hydroxyglucalester 2, the others being the selective hydroxylaminolysis of the enol ester group 2→3, Zemplén de-O-acylation, and deoximation (3→4→1) (Scheme 1). Since then, various other enzymatic and chemical 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).

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 by conversion of maltose, cellobiose, and lactose, via their 2-hydroxyglycal esters into the respective perbenzoylated 4-O-glycosyl-1,5-anhydrofructoses with yields in the 70% range for the four steps involved (Scheme 2). The lactose-derived 6c was even deoximated to the respective, highly crystalline ulose monohydrate 7.

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

Scheme 2. Disaccharide-derived 1,5-anhydrofructose derivatives.
Apparently unaware of this expedient, large scale adaptable access to 4-O-glycosylated 1,5-anhydrofructoses, recently, Agoston et al. patented and published another approach comprising of the glycosylation of a bicyclic 1,5-anhydrofructose derivative with glycosyl trichloracetimides, an inconvenient route due to the 11 steps required, three for the donor substrate; five for the acceptor; and another three for the targets with overall yields of around 15%.

Due to potential medical applications, 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 transglycosylation was deemed suitable for conjugation with proteins and as antioxidant food additives. Since their generation via 2-hydroxyglycal 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 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, it appeared obvious to generate glycosylated analogues of 1 from disaccharide-derived 2-hydroxyglycal 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 α-glucose, obviously originating from base induced β-elimination, a reaction readily occurring with 2-hydroxyglycal esters under mild basic conditions. As chromatographic purification proved quite laborious, this access was not elaborated.

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

Application of the three-step sequence hydroxylaminolysis, de-O-acetylation and deoxygenation to any of the disaccharide-derived 2-hydroxyglycal 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-1,5-anhydrofructose E-oximes 6a–6e isolable in excellent yields of 85–90%.

That these products invariably have their N-OH group oriented towards 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.

The release of the free glycosyl-(1→4)-1,5-anhydrofructoses 9f-9h from their oximes proceeded in the expected manner: de-O-acetylation 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 equilibriums. 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. Although separable by chromatography due to the sufficiently different Rf values, the E/Z-oxime mixtures 8f–8h were directly subjected to transglycosylation 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 (C12H20O10·H2O) or 2,2-dihydroxy forms, as indicated in the formulæ. Unequivocal structural proof followed from their 1H and 13C NMR spectra of 8f–9h in D2O (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-(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, 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. products represent dihydrates, as evidenced by essentially perfect analytical values for C12H20O10·2H2O (or C9H12O11·H2O 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-tagatose prepared in the same way. They analyze for monohydrates, whereas 1,5-anhydro-o-tagatose exhibits a pronounced tendency to adapt the 2-carboxyl form in aqueous solution and in the solid state. 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, when acquiring these products from glucose and fructose, respectively.

Table 1

| Compound | R1 | R2 | Solvent | H-1e | H-1a | H-3 | H-4 | NOH | H-1' | J1,J1 | J1,J2 | J1,Jz | J1,z | Ref. |
|----------|----|----|---------|------|------|-----|-----|-----|------|-------|-------|-------|-------|------|------|
| 3a       | Bz | Bz | DMSO-d6 | 5.13 | 4.28 | 6.13 | 5.63 | 11.35 | —    | 14.8  | 8.4   | 8.8   | —     |       | 3b   |
| 6a       | GlcBz4 | Bz | CDCl3 | 4.92 | 4.48 | 5.91 | 5.45 | 8.29 | 5.62 | 16.7  | 3.8   | 10.3  | 3.9   |       |      |
| 6b       | GlcBz4 | Bz | CDCl3 | 4.83 | 4.23 | 6.03 | 4.20 | 8.54 | 5.11 | 16.5  | 4.0   | 8.2   | 8.0   |       |      |
| 6c       | GlcBz4 | Bz | CDCl3 | 4.98 | 4.32 | 6.18 | 4.36 | 8.40 | 5.18 | 16.4  | 4.5   | 8.1   | 8.0   |       |      |
| 3b       | Ac | Ac | DMSO-d6 | 4.88 | 4.04 | 5.54 | 4.94 | 11.48 | —    | 15.0  | 8.0   | 8.9   | —     |       | 3b   |
| 6d       | GlcAc4 | Ac | CDCl3 | 4.85 | 4.20 | 5.27 | 3.85 | 8.23 | 5.14 | 16.5  | 4.5   | 7.7   | 4.0   |       |      |
| 6e       | GlcAc4 | Ac | CDCl3 | 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, only 100 MHz data were given.
1,5-anhydro-D-fructose and its analogues were synthesized and characterized. Significant 1H and 13C NMR data (500 resp. 75.5 MHz in D2O) for the monohydrates of 1,5-anhydro-α-fructose and its 4-O-glycosyl derivatives 9f-9h are provided.

Table 2: Significat 1H and 13C NMR data (500 resp. 75.5 MHz in D2O) for the monohydrates of 1,5-anhydro-α-fructose and its 4-O-glycosyl derivatives 9f-9h

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* Not unequivocally 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. 1H and 13C NMR spectra were recorded on Bruker ARX 300 and Avance 500 instruments. Mass spectra were measured on a VG ZAB 2 mass spectrometer, microanalyses on a Perkin-Elmer 4000 elemental analyzer. Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F254 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-α-fructose f-oxime 6d

To a solution of NH2OH·HCl (2.4 g, 35 mmol) in pyridine (100 mL) were added 6.2 g (10 mmol) of 2-acetoxy-cellobial hexaacetate 5d and the mixture was stirred at ambient temperature until the educt had disappeared (ca. 24 h, R1 = 0.33–0.21 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 CHCl3 (150 mL each), followed by separation and extraction of the water layer with CHCl3 (2 × 100 mL). The combined CHCl3 extracts were washed with ice-cold 1 M HCl solution and water, dried (MgSO4), 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; [α]D = –61.4 (c 1.0, CHCl3); 1H NMR (500 MHz, CDCl3): 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-1), 4.01 and 4.17 (two 1H-dd, 6-H2), 4.11 and 4.31 (two dd, 6-H2), 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); J1,1 = 16.5, J3,4 = 4.5, J4,5 = 7.7, J5,6 = 2.3 and 4.5, J6,6′ = 12.4, J1,2 = 4.0, J2,3 = 10.4, J3,4 = J4,5 = 9.6, J5,6 = 2.7 and 6.3, J6,6′ = 12.1 Hz. 13C NMR (75.5 MHz, CDCl3): δ 20.9–21.2 (6 AcCH2), 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, C-4′), 95.8 (C-1′), 151.9 (C-2′). Anal. Calc. for C39H41NO16 (591.51): C, 48.73; H, 5.62; N, 2.37. Found: C, 48.81; 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-α-fructose f-oxime 6e

Hydroxylaminolysis of 2-acetoxy-cellobial hexaacetate 5a (10.2 g, 16.4 mmol) was effected by stirring in pyridine (100 mL) containing NH2OH·HCl (10.0 g, 0.15 mol) for about 24 h at room temperature (R1 = 0.27–0.16 in 2:1 toluene–EtOAc). Work-up as described above for 6d gave a sirupy residue crystallizing from...
EtOH: 8.24 g (85%) of 6c in two crops; colorless needles of mp 159–161 °C; [α]D20 = −29.9 (c 1.0, CHCl3). 1H NMR (500 MHz, CDCl3): δ 2.00–2.10 (six 3H-s, 6 Ac-CH3), 3.51 (1H-idd, H-5), 3.78 (1H-idd, H-5′), 3.83 (1H-dd, H-4), 4.09 and 4.11 (two 1H-dd, H-6a and H-6b), 4.26 (1H-dd, H-1α), 4.30 and 4.31 (two 1H-dd, H-6b and H-6′), 4.70 (1H-idd, H-1′), 4.90 (1H-idd, H-1′), 4.97 (1H-idd, H-2′). 5.08 (1H- tt, H-3′), 5.19 (1H-tt, H-4′), 5.73 (1H-2d, H-5′), 8.71 (1H-2d, H-6′). J1,1 = 16.4, J3,4 = 4.4, J3,5 = 8.1, J3,3 = 2.6 and 49, J3,6 = 11.9, J1,2 = 8.1, J2,3 = J4,5 = 9.5, J6,3 = 4.9 and 6.1, J6,6 = 12.0 Hz. 13C NMR (75.5 MHz, CDCl3): δ 20.5–20.7 (Ac3CH), 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. Calc for C24H33NO16 (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-α-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 iPrOH/EtOAc/water showed complete conversion of the educt into an approximate 2.5:1 mixture of E/Z-isomers (1H NMR) of R = 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 solvent, finally at 0.1 Torr: 1.78 g (83%) of 8f in 66% yield.

Whilst these 1H and 13C 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 C12H20O10 9g (sum formula given in Ref. 9), which factually is a dihydrate (calc for C12H20O9·2H2O: C, 40.00; H, 4.71). These peculiar incongruities remain to be clarified.

De-O-benzylation 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.

4.5. 4-O-(α-D-Glucopyranosyl)-1,5-anhydro-α-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, D2O): 5.20 (1H-dd, J1,2 = 3.8 Hz, H-1′), 5.12 (1H-dd, J3,4 = 3.8 Hz, H-3′), 4.90 and 4.20 (two 1H-dd, J1,2 = 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. Calc for C24H33NO16·H2O (591.50): C, 48.73; H, 5.51; N, 2.30.

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 iPrOH/EtOAc/water revealed products at Rf = 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-1α at 4.95 ppm; minor: H-3 as 3.4 Hz-d at 5.02, H-1α at 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. [α]D20 = −21.2 (c 1.0, water); 1H NMR (500 MHz, D2O, 3 h after dissolution): δ 4.40 (1H-dd, J1,2 = 7.9 Hz, H-1′), 3.90 and 3.75 (two 1H-dd, H-6, H-6′), 3.70 and 3.42 (two 1H-dd, J1,2 = 12.1 Hz, H-1α and H-1β), 3.60 (1H-tt, H-3′, H-3′), 3.40 (br 4H-m, H-5, H-3′–H-5′), 3.26 (1H-m, H-2′). 13C NMR (D2O): 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. Calc for C12H20O9·H2O (342.30): C, 42.10; H, 6.48. Found: C, 42.02; H, 6.50.

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/Methanol 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 D2O: H-3α 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; [α]D20 = −22.3 (c 0.8, water); 1H NMR (500 MHz, D2O): δ 4.35 (d, 1H, J1,2 = 7.9 Hz, H-1′), 3.78–3.62 (complex m, 6H, H-6, H-6′, H-5, H-5′), 3.59 and 3.30 (two 1H-dd, J1,2 = 12.0 Hz, H-1α and H-1β), 3.50 (3H-m, H-3′, H-3″); H-4″),
~3.40 (2H-m, H-4, H-2'). 13C NMR (75.5 MHz, D2O): 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 C12H20O10·D2O (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 C12H22O10·H2O,9 which de
facto is a dihydrate C12H20O9·2H2O (calcd C, 40.00; H, 6.71).

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