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Note

1,5-Anhydro-D-fructose from D-fructose

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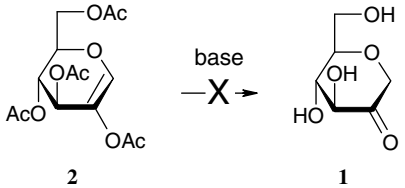
Abstract—1,5-Anhydro-D-fructose was efficiently prepared from D-fructose via regiospecific 1,5-anhydro ring formation of 2,3-*O*-isopropylidene-1-*O*-methyl(tolyl)sulfonyl-D-fructopyranose and subsequent deprotection.

Keywords: 1,5-Anhydro-D-fructose; Synthesis

1,5-Anhydro-D-fructose, AF, (**1**) is a versatile naturally occurring monosaccharide and chiral building block featuring interesting chemical as well as biological properties.[1] Due to its structural features, synthetic approaches have been met with limited success. Compound **1** has not been available until 1980 despite the fact that its protected derivatives such as 2-acyloxyglycals **2** have been known (Scheme 1),[2] but their attempted direct conversion into compound **1** by base-catalysed deacylation[3–6] gave a complex mixture of (degradation) products.[6]

Employing various experimental detours, 1,5-anhydro-D-fructose (**1**) was finally synthesised in low overall yield by Lichtenthaler and co-workers from 1,5-anhydro-2,3,4,6-tetra-*O*-benzoyl-D-*arabino*-hex-1-enitol **3** (Scheme 2) in 1980.[7]



2 **1**

Scheme 1.

No direct structural proof of the obtained product was given, but dimeric forms were mentioned.[7]

In 1988, a different synthetic route to AF was patented, which was based upon the oxidation of the C-2 hydroxyl function in a partially protected 1,5-anhydro-D-glucitol derivative **11**, available from **9** by standard procedures (Scheme 3).[8]

In 1988, a glucan lyase which degrades starch and related oligosaccharides from the non-reducing end of the oligosaccharides to give 1,5-anhydro-D-fructose was identified.[9] Since, several other lyases isolated from different sources have also been found to catalyse this process.[1]

In 1993, a pyranose 2-oxidase catalysed oxidation of 1,5-anhydro-D-glucitol **9** was reported[10] and in 1998 a process furnishing **1** on a preparative scale in 98% yield based on this method was published.[11]

Exploiting Baute's[9] enzymatic method, AF was prepared from starch in 40–50% yield in a process which has attracted commercial interest.[12–14] The enzyme has also been cloned and expressed in *Aspergillus niger* providing a basis for a more efficient and industrially compatible production strategy.[15,16]

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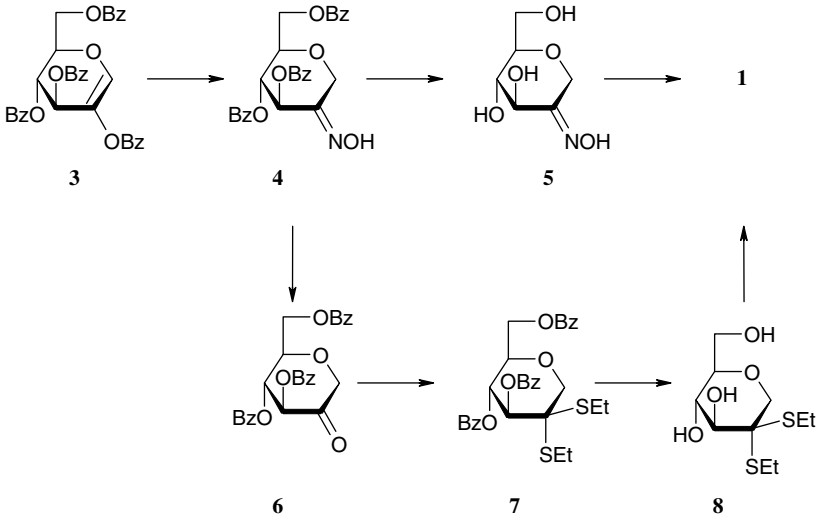
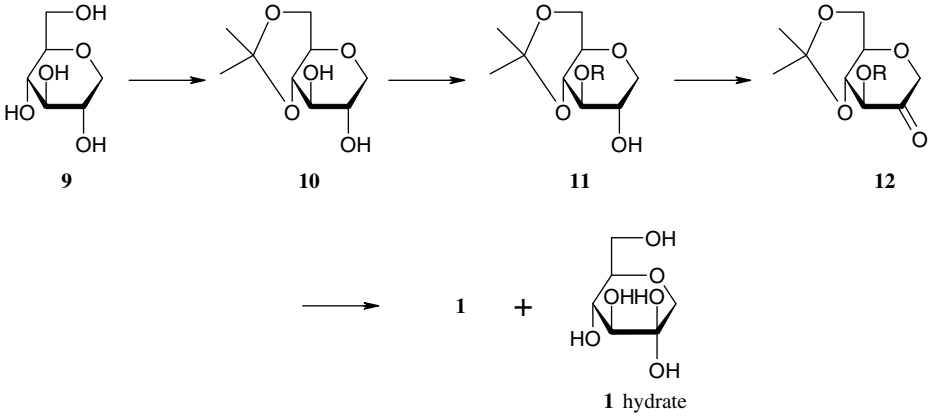


Scheme 2.



Scheme 3.

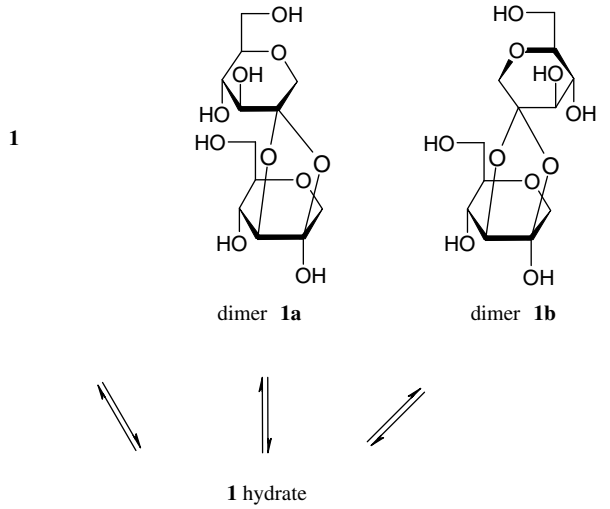
1,5-Anhydro-D-fructose has never been reported in a pure monomeric form. Due to its presumably hygroscopic nature it has been isolated as mixtures consisting of monomeric and dimeric forms[17,18] or the monomeric and the hydrated form (Scheme 4).[10,17]

Only very few derivatives of AF have become known. Amongst these are fatty acid esters at C-6 which were prepared by regioselective chemical as well as enzymatic methods by Lundt and co-workers,[19] α-D-glucopyranosides at this position[20] as well as at C-3[21] obtained by enzymatic glycosyl transfer. Due to the high base sensitivity of the unprotected parent compound, other substituted derivatives have been difficult to prepare.

It has been demonstrated that 1,5-anhydro-D-fructose is a powerful antioxidant and antimicrobial agent.[22,23] Moreover, an aqueous solution of AF is very stable under neutral conditions and is, unlike L-ascorbic acid, not oxidised by molecular oxygen.[24] Thus, 1,5-anhydro-D-fructose might find potential applications in the food industry[22,23,25–27] (preventing pigment discolouration, enzymic browning, protecting flavour, aroma and nutrient content, extending shelf life), cosmetics industry[28] (replacing the unstable L-ascorbic acid) and pharmaceutical industry (stimulating hormone secretion of insulin and glucagon-like peptide 1 (GLP 1)).[29,30]

Intriguingly, it has also been proven that in mammals and humans, glycogen degrades by α-(1→4)-glucan lyase to 1,5-anhydro-D-fructose[31,32] which subsequently is reduced to 1,5-anhydro-D-glucitol by a NADPH-dependent 1,5-anhydro-D-fructose specific reductase.[33] This constitutes a third glycogenolytic pathway, in addition to the phosphorolytic and hydrolytic degradation cascades.[31]

In spite of these interesting biological properties and of the impressive progress made in enzymatic preparation of AF, the product is neither available at bulk scale nor has it been commercially utilised, presumably due to the lack of an efficient and cost-efficient preparation of this compound.



Scheme 4.

Consequently, 1,5-anhydro-D-fructose and its derivatives are attractive products bearing substantial industrial and commercial potential provided scaleable and efficient approaches are at hand.

We considered D-fructose, a cheap and abundant renewable sugar a suitable starting material for a new approach towards 1,5-anhydro-D-fructose (Scheme 5).

D-Fructose, via easily available 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**13**, 85%) was converted into known[34] tosylate **14** (95%) by standard procedures. Alternatively, the known[35] corresponding 1-mesylate **15** was prepared (95%) allowing for considerably shorter reaction times.

The regioselective removal of the 4,5-*O*-isopropylidene moiety in the presence of the 2,3-acetal turned out to be the crucial step of the synthesis and, after several pitfalls employing a large variety of different acidic catalysts, could be achieved best exploiting oxalic acid in 85% aqueous acetonitrile at reflux temperature furnishing around 50% of the desired intermediate **16** from tosylate **14**. Under optimised conditions, the corresponding 1-mesylate **15** gave 73% of desired product **17** and most of the remaining starting material could be recovered allowing for 'yields by conversion' of well over 90% in this particular step.

Intramolecular anhydro ring closure was found a straightforward process employing sodium hydride in *N*,*N*-dimethylformamide (75% from tosylate **16**). Improvements of the reaction conditions employing aqueous sodium hydroxide at gentle reflux for 15 min allowed access to 1,5-anhydro-D-fructose derivative **18** in 90% isolated yield.

Deprotection of acetal **18** with 80% aqueous acetic acid at 65 °C for 15 min gave compound **1** in an isolated yield of 94%.

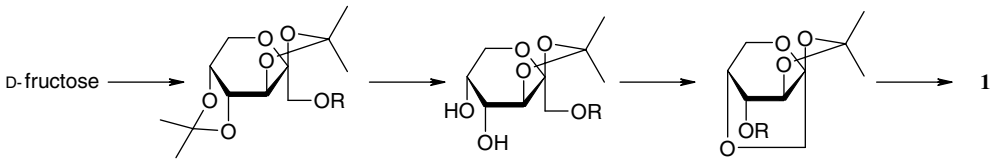
This sequence comprises of five simple steps employing inexpensive starting material and chemicals. Despite our best efforts, the overall yield from D-fructose via 5-tosylate **14**, was only 28%.

Gratifyingly, exploiting mesylate **15** together with slightly modified procedures as given in Section 1, 1,5-anhydro-D-fructose (**1**) is available from D-fructose in 50% overall yield at a scale of 10–100 g in each step, demonstrating the potential for scaling up. Another redeeming feature of the extremely simple sequence presented is the regioselective en route accessibility of O-4 in partially protected compound **18**, allowing for a wide variety of defined modifications at this position with a view to the feasible applications of such products as mentioned in the introduction.

1. Experimental

1.1. General methods

Melting points were recorded on a Tottoli apparatus and are uncorrected. Optical rotations were measured on a JASCO Digital Polarimeter or with a Perkin Elmer 341 with a path length of 10 cm. NMR spectra were recorded at 200 as well as 500 MHz (^{1}H), and at 50 and 125 MHz (^{13}C). Chemical shifts are listed in δ employing residual, not deuterated, solvent as the internal standard. The signals of the protecting groups and of aromatic substituents were found in the expected regions and are not listed explicitly. Structures of crucial intermediates were unambiguously assigned by 1D-TOCSY and HSQC experiments. Electrospray mass spectra were recorded on an HP 1100 series MSD, Hewlett Packard.



Scheme 5.

Samples were dissolved in acetonitrile/MeOH mixtures. The scan mode for negative ions (mass range 100–1000 D) was employed varying the fragmentation voltage from 30 to 130 V. TLC was performed on precoated aluminum sheets (E. Merck 5554). Compounds were detected by staining with concd H_2SO_4 containing 5% vanillin.

1.2. 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose (13), 2,3:4,5-di-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-β-D-fructopyranose (14), and 2,3:4,5-di-*O*-isopropylidene-1-*O*-methylsulfonyl-β-D-fructopyranose (15)

Compounds (**13**), (**14**) as well as (**15**) were prepared following known[34,35] procedures.

1.3. 2,3-*O*-Isopropylidene-1-*O*-*p*-tolylsulfonyl-β-D-fructopyranose (16)

To a soln of compound **14**[34] (99 g, 239 mmol) in 85% aq MeCN (1.2 L), oxalic acid (24 g, 192 mmol) was added and the mixture was kept under reflux for 48 h. Solid $NaHCO_3$ was added until pH 7, the mixture was filtered and the filtrate was concentrated under diminished pressure. The remaining material was washed with CH_2Cl_2, the organic layer was dried (Na_2SO_4), filtered and concentrated under diminished pressure. The remaining crystals were dried to give compound **16** (40 g, 45%): mp 82–85 °C, $[\alpha]_D^{20}$ +16 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (MeOH-d_4): δ 4.18 (d, 1H, $J_{1a,1b}$ 10.4 Hz, H-1a), 4.14 (d, 1H, H-1b), 4.07 (br s, 2H, H-3, H-4), 3.90 (m, 1H, H-5), 3.54 (m, 2H, H-6a, H-6b); ^{13}C NMR: δ 100.3 (C-2), 77.3, 66.9, 66.7, 63.6, 62.7 (C-1, C-3, C-4, C-5, C-6). Anal. Calcd for $C_{16}H_{22}O_8S$: C, 51.33; H, 5.92. Found: C, 51.27; H, 5.97.

The starting material **14** (29.8 g, 30%) could be recovered from the mother liquor.

1.4. 2,3-*O*-Isopropylidene-1-*O*-methylsulfonyl-β-D-fructopyranose (17)

A mixture of compound **15**[35] (40 g, 118 mmol) and oxalic acid (8.5 g, 94 mmol) was kept under reflux in MeCN/water [600 mL, 5:1 (v/v)] for 28 h. The reaction was allowed to cool and 25% aq ammonia (16 mL) was added slowly over 5 min. The resulting suspension was stirred at 0 °C for 30 min, then filtered. The precipitate was washed with MeCN (100 mL). The filtrate and the washing were combined and the solvent was removed under diminished pressure. The remaining residue was taken up into CH_2Cl_2 (200 mL) and the resulting soln was filtered and washed with distilled water (20 mL). The aq phase was extracted with CH_2Cl_2 (3×200 mL). The combined aq layers were concentrated under diminished pressure to give crude product **17** as a syrup. This was dissolved in 1:1 EtOAc–petroleum ether and the mixture was stirred vigorously at ambient temperature. The suspension thus obtained was cooled to 0 °C and stirred for another 2 h. Filtration gave product **17** (19 g, 71%): mp 90–94 °C, $[\alpha]_D^{20}$ +13 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (acetone-d_6): δ 4.35 (m, 2H, H-1a, H-1b), 4.16 (m, 2H, H-3, H-4), 3.95 (ddd, 1H, $J_{4,5}$ 3 Hz, $J_{5,6a}$ 2.8 Hz, $J_{5,6b}$ 2 Hz, H-5), 3.70 (dd, 1H, $J_{6a,6b}$ 11.5 Hz, H-6a), 3.64 (dd, H-6b); ^{13}C NMR: δ 100.5 (C-2), 76.9, 67.2, 67.1, 63.7, 63.0 (C-1, C-3, C-4, C-5, C-6). HRAPIESIMS (neg. mode): [M−H] calcd for $C_{10}H_{18}O_8S$ 374.4061, found 373.410. Anal. Calcd for $C_{10}H_{18}O_8S$: C, 40.26; H, 6.08. Found: C, 40.21; H, 6.13.

A second crop (0.7 g, 2.6%) was obtained from processing of the mother liquor. The CH_2Cl_2 phase was concentrated under diminished pressure to give unreacted starting material **15** (10 g, 25%).

1.5. 1,5-Anhydro-2,3-*O*-isopropylidene-β-D-fructopyranose (18)

Method A: To a soln of tosylate **16** (66.4 g, 176 mmol) in DMF (1.5 L), NaH (15 g) was added and the mixture was stirred at ambient temperature for 2 h. Water was added, solvents were removed under diminished pressure and the remaining residue was treated with CH_2Cl_2. The soln was filtered over a plug of celite and the solvent was removed under diminished pressure.

Crystallisation from ether furnished 1,5-anhydrosugar **18** (26.9 g, 75%): mp 110–113 °C, $[\alpha]_D^{20}$ +18 (*c* 0.8, MeOH); ^{1}H NMR (MeOH-d_4): δ 4.28 (d, 1H, $J_{1a,1b}$ 9.0 Hz, H-1a), 4.19 (dd, 1H, $J_{5,6a}$ 1.5 Hz, $J_{6a,6b}$ 10.2 Hz, H-6a), 4.16 (d, 1H, $J_{3,4}$ 3.6 Hz, H-3), 3.99 (d, 1H, H-4), 3.97 (dd, 1H, $J_{5,6b}$ 1.5 Hz, H-6b), 3.86 (d, 1H, H-1b), 3.85 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 115.6 (C-1′), 99.4 (C-2), 87.8, 77.0, 74.6, 73.9, 71.2, 66.9 (C-1, C-3, C-4, C-5, C-6), 28.0 (C-2′a), 25.8 (C-2′b). HRAPIESIMS (neg. mode): [M−H] calcd for $C_9H_{14}O_5$ 202.2045, found 201.190. Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.40; H, 7.01.

Method B: Compound **17** (30 g, 100 mmol) was added to a soln of NaOH (7.24 g) in water (83 mL). The reaction mixture was stirred under gentle reflux for 15 min, then cooled in an ice bath and slowly acidified to pH 6 by addition of 10% aq HCl. Aq ammonia (2 mL, 25%) was added and the solvent was removed under diminished pressure. The residue was vigorously stirred with $CHCl_3$ (500 mL) at ambient temperature for 20 min, then filtered. The residue was washed with $CHCl_3$ (300 mL). Combined organic layers were concentrated under diminished pressure and the resulting solid residue was stirred with toluene (150 mL) under reflux for 30 min, then brought to ambient temperature. The cloudy suspension was stirred at 0 °C for 2 h and the precipitate was collected by filtration and tried to give anhydrofructose derivative **18** (18 g, 90%).

For further characterisation, **18a** was prepared by conventional O-acetylation employing acetic anhydride in pyridine to give crystalline acetate: $[\alpha]_D^{20}$ +5.3 (*c* 0.85, CH_2Cl_2), mp 98–102 °C; ^1H NMR ($CDCl_3$): δ 5.16 (d, 1H, $J_{3,4}$ 4.2 Hz, H-4), 4.36 (d, 1H, $J_{1a,1b}$ 9.0 Hz, H-1a), 4.27 (dd, 1H, $J_{5,6a}$ 1.5 Hz, $J_{6a,6b}$ 10.2 Hz, H-6a), 4.22 (d, 1H, H-3), 4.13 (dd, 1H, $J_{5,6b}$ 1.5 Hz, H-6b), 4.05 (br s, 1H, H-5), 3.95 (d, 1H, H-1b); ^{13}C NMR: δ 170.6 (C=O), 99.2 (C-2), 83.7, 77.0, 71.3, 71.1, 66.9 (C-1, C-3, C-4, C-5, C-6), 21.2 (COMe). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.03; H, 6.66.

1.6. 1,5-Anhydro-D-fructopyranose (1)

A soln of compound **18** (10 g, 49.5 mmol) in aq acetic acid (80%, 30 mL) was stirred at 65 °C for 15 min and the solvent was removed under diminished pressure. The residue was dissolved in dry MeOH (50 mL) and the soln was slowly added to cold ether (1000 mL) under vigorous stirring. The resulting suspension was stirred at 0 °C for 2 h and filtered. The precipitate was washed with dry ether (300 mL) and dried under diminished pressure to give known final product to give **1** (8 g, 94%) as a hygroscopic white powder. The product showed a ^{13}C NMR spectrum identical with that of an authentical sample of **1** provided by Danisco (Copenhagen) and prepared according to Refs. 12 and 14: ^{13}C NMR (**1** hydrate, D_2O): δ 92.8 (C-2), 80.8, 77.1, 71.9, 69.1, 61.4 (C-1, C-3, C-4, C-5, C-6); for comparative data, see Refs. 17 and 18.

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