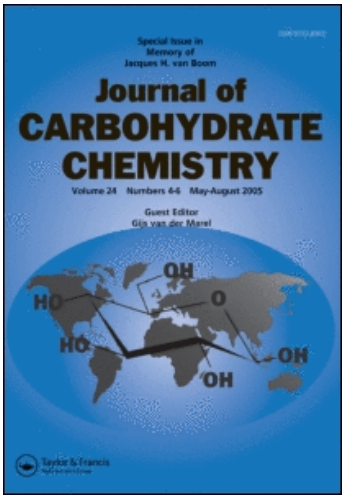

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1,5-ANHYDRO-D-FRUCTOSE: STEREOSELECTIVE CONVERSIONS TO 1,5-ANHYDROALDITOLS AND DEOXY/AMINO SUBSTITUTED ANALOGUES

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ABSTRACT

1,5-Anhydro-D-fructose (**1**) has been converted into crystalline oximes. 1,5-Anhydroalditols and 2-amino-2-deoxy-1,5-anhydroalditols have been prepared by stereoselective reduction procedures from **1** and from the oximes, respectively.

INTRODUCTION

1,5-Anhydro-D-fructose (**1**), prepared for the first time in 1980 by a multistep synthesis,[1] is now available in larger amounts by enzymatic degradation of α-1,4-glucans.[2,3,4] Recently, we have proved by means of X-ray crystallography,[5] that **1** adopts the dimeric structures **1a** and **1b** in anhydrous solvents, and similar results have been obtained through NMR studies.[6] In water 1,5-anhydro-D-fructose is present as the hydrate **1c** (Figure 1).[7] The chemistry of 1,5-anhydro-D-fructose (**1**), as well as that of 1,5-anhydrohex-2-uloses in general, is poorly understood. We have now performed a detailed

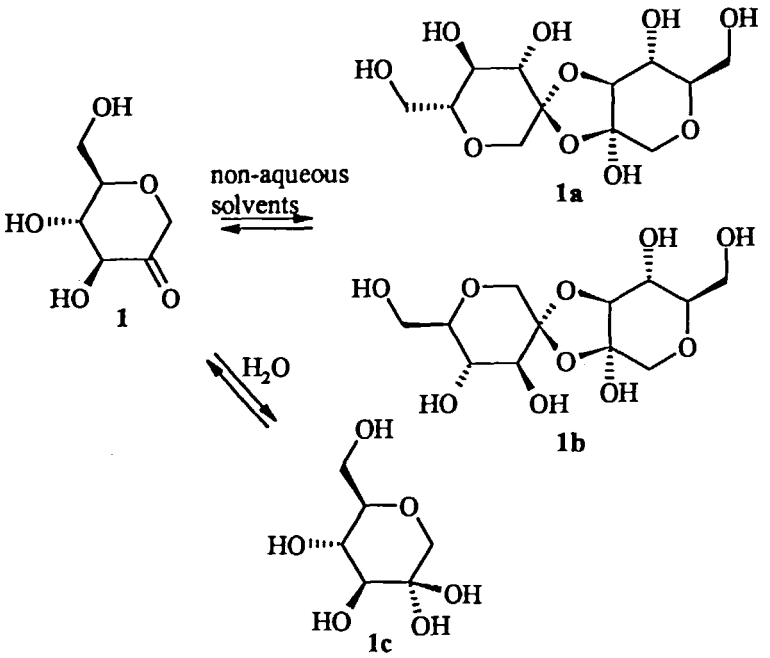


Figure 1.

examination of some fundamental reactions of **1** in order to evaluate it as a chiral starting material.

RESULTS AND DISCUSSION

Previously, we have described that acylation of 1,5-anhydro-D-fructose (**1**) in pyridine gave mixtures due to the presence of two dimeric forms, **1a** and **1b**, in addition to the monomeric form **1** in this solvent.[5] Acetylation of **1** in a mixture of acetic anhydride/ pyridine gave the acetylated enolone **2** since the peracetylated monomeric 1,5-anhydro-D-fructose eliminated acetic acid under the reaction conditions. Compound **2** could be isolated in 55% yield.[5] Thus, acetylation of 1,5-anhydro-D-fructose (**1**) yields a highly functionalised chiral synthon in one step.

The enolone **2** has already proven to be a versatile chiral building block, since it was used in the synthesis of the natural products palythazin[8] and bissetone.[9] In connection with the latter synthesis the Diels-Alder reaction and Michael addition to the conjugated ketone **2** have been exploited.[9] We have now investigated hydrogenation of the

unsaturated moieties of **2** and of the corresponding oximes **5** and **6** under various reaction conditions in order to obtain 1,5-anhydroalditols and 2-amino-2-deoxy-1,5-anhydroalditols. Such compounds are of importance in different respects. 1,5-Anhydroalditols have proven to be of interest for industrial uses such as the synthesis of non-ionic surfactants.[10] In addition, the tetrahydropyran ring of 1,5-anhydroalditols is one of the main structural features of hydroxylated polyether antibiotics.[11,12] Finally, the 2-amino-2-deoxy-1,5-anhydroalditols have shown biological activity as appetite depressants[13] and have been used for the synthesis of sugar modified oligonucleotides.[14]

Thus, when **2** was kept in a hydrogen atmosphere for 1½ h in the presence of 5% Pd/C as a catalyst, the carbon-carbon double bond was reduced exclusively to give the saturated ketones **3** and its C-3 epimer in a 6:1 ratio. Upon addition of diethyl ether the saturated ketone **3** with D-*threo*-configuration crystallised in 39% yield. By increasing the hydrogen pressure to 3 KPa and prolonging the reaction time, the saturated hexitol **4** was formed as the main product. Two chiral centers were formed stereoselectively during saturation of the conjugated ketone **2**. The partially protected hexitol **4**, having the D-*lyxo*-configuration, was isolated in 49% yield after chromatography. By recharging the catalyst, the yield could be increased to above 90% (Scheme 1). The configurations of the new chiral centers in **3** and **4** were unambiguously determined by ^{1}H NMR spectroscopy (Table 2).

Since 1,5-anhydro-D-fructose (**1**) adopts dimeric structures (Figure 1), we have investigated reactions of the C-2 carbonyl group, in order to obtain identical products from both the monomeric and dimeric forms of 1,5-anhydro-D-fructose (**1**). Attempts to obtain monomeric ketals of **1** by reaction with either methanol or ethylene glycol under acidic conditions gave mixtures of monomeric and dimeric forms. In contrast, reactions with hydroxylamine or *O*-benzylhydroxylamine afforded oximes of monomeric **1** exclusively and in high yields. Thus, treatment of **1** with 1 equiv of hydroxylamine afforded the crystalline oxime **5** in 66% yield. Similarly, by reaction of **1** with 1 equiv of *O*-benzylhydroxylamine, crystalline 1,5-anhydro-D-fructose *O*-benzyloxime (**6**) was isolated in 91% yield.

Thus, monomeric forms of **1** could be trapped either as the oximes **5** and **6** or as the hydrate **1c** in water. Investigation of reduction of these compounds was undertaken.

Catalytic reduction of the oxime **5** afforded the *manno*-configured aminosugar **7** stereoselectively as a crystalline product in 72% yield. Hydrogenation of an aqueous solution of 1,5-anhydro-D-fructose (**1**), with a catalytic amount of 5% Pd/C, yielded the naturally occurring 1,5-anhydro-D-mannitol (styracitol) (**8**) and the C-2 epimer, 1,5-anhydro-D-glucitol (**9**), in a 4:1 ratio. Upon addition of ethanol, **8** crystallised in 58% yield. In contrast, reduction of **1c** with $NaBH_4$ gave a product mainly having a *gluco*-configuration. Thus, the naturally occurring 1,5-anhydro-D-glucitol (polygalitol) (**9**) and the C-2 epimer, 1,5-anhydro-D-mannitol (**8**), were formed in a 4:1 ratio. Upon addition of ethanol, **9** crystallised in 60% yield. Compared to previously reported procedures[15] simple and very efficient routes to 1,5-anhydro-D-mannitol (**8**) and 1,5-anhydro-D-glucitol (**9**) have now been developed. The stereoselectivity in reduction of the carbonyl group was determined by the reducing agent, since catalytic hydrogenation afforded the alditol with the *manno*-configuration while $NaBH_4$ afforded the one with the *gluco*-configuration.

Table 1. ^{13}C NMR data.[a]

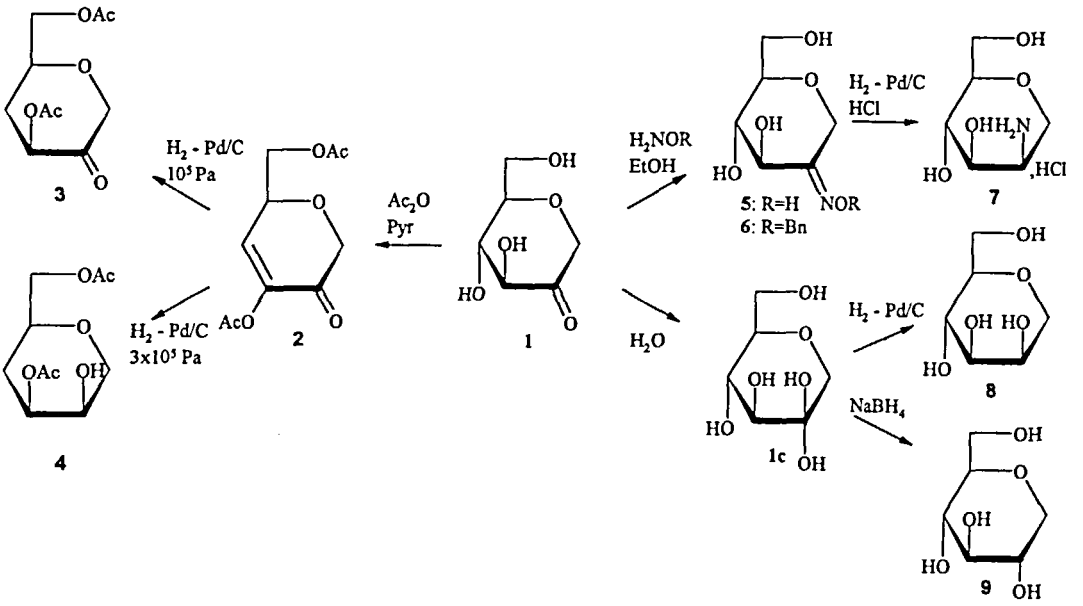
Compound	C-1	C-2	C-3	C-4	C-5	C-6
3[b]	73.6	199.3	72.4	34.7	73.2	65.3
4[b]	70.3	65.9	71.3	27.7	73.9	66.2
5[c]	61.5	156.5	73.3	72.6	80.8	61.9
6[d]	62.6	157.0	74.3	73.7	82.1	63.1
7[c]	66.5	53.2	70.8	67.4	81.6	61.5
8[c]	70.6	69.9	74.3	68.1	81.3	62.0
9[c]	69.6	70.2	78.3	70.5	81.1	61.7

a. δ-values (ppm) for **5-9** (62.9 MHz) and for **3**, **4** (125.8 MHz); signals assigned by C-H correlated NMR.
b. $CDCl_3$ (δ 77.0 ppm).
c. D_2O (dioxane as internal standard at δ 67.4 ppm).
d. MeOH-d_4 (δ 49.0 ppm).

In conclusion, we have shown that 1,5-anhydro-D-fructose (**1**) is a versatile chiral starting material for the synthesis of optically 1,5-anhydroalditols and 2-amino-2-deoxy-1,5-anhydroalditols.

EXPERIMENTAL

General methods. 1,5-Anhydro-D-fructose was freeze-dried from an aqueous solution. Residual water was co-evaporated with toluene 3 times before use. All solvents



Scheme 1

were distilled before use. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker instruments AC 250 (ambient temperature) and AM 500 (300 K). For NMR spectra the solvent peak was used as reference. The signals were assigned by COSY and C-H correlated NMR spectroscopy. Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Microanalyses were carried out by the Microanalytical Department, University of Copenhagen and the Research Institute for Pharmacy and Biochemistry, Prague. HRMS was carried out by the Chemistry Department, University of Copenhagen. TLC was performed on plates precoated with kieselgel 60 F_{254} and spots were visualised by spraying with a mixture of 1.5% (w/w) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 1% (w/w) $Ce(SO_4)_2{\cdot}4H_2O$ and 10% (v/v) H_2SO_4, followed by heating. Flash chromatography was performed on silica gel 60 (Grace AB Amicon, 35-70 μm). Evaporations were performed *in vacuo* at temperatures below 45 °C.

3,6-Di-*O*-acetyl-1,5-anhydro-4-deoxy-D-*threo*-hex-2-ulose (3). The unsaturated ketone **2**[5] (0.420 g, 1.8 mmol) was dissolved in EtOAc (20 mL) and hydrogenated at 10^5 Pa in the presence of 5% Pd/C (50 mg). After 1½ h the catalyst was filtered off and the filtrate dried ($MgSO_4$) and concentrated to a syrup (0.410 g, 97%), which was shown by ^{1}H NMR to contain **3** and the C-3 isomer in a 6:1 ratio. Upon addition of Et_2O **3**

Table 2. ^{1}H NMR data.[a]

Compound	3[b]	4[b]	5[c]	6[d]	7[c]	8[c]	9[c]
H-1a	4.22 (d)	4.05 (dd)	5.05 (d)	5.03 (d)	4.03 (dd)	3.87 (dd)	3.92 (dd)
	$J_{1a,1b}$ 15.0	$J_{1a,1b}$ 12.5	$J_{1a,1b}$ 14.5	$J_{1a,1b}$ 15.0	$J_{1a,1b}$ 13.5	$J_{1a,1b}$ 12.0	$J_{1a,1b}$ 11.0
		$J_{1a,2}$ 2.5			$J_{1a,2}$ 1.5	$J_{1a,2}$ 2.0	$J_{1a,2}$ 5.5
H-1b	4.09 (dd)	3.58 (dd)	3.90 (d)	3.91 (d)	3.78 (dd)	3.59 (dd)	3.21 (t)
	$J_{1b,3}$ 1.0	$J_{1b,2}$ 1.0	$J_{1b,5}$ 0.5		$J_{1b,2}$ 1.5	$J_{1b,2}$ 1.0	$J_{1b,2}$ 11.0
H-2	-	3.91 (dddd)	-	-	3.66 (ddd)	3.93 (ddd)	3.52 (ddd)
		$J_{2,3}$ 2,5			$J_{2,3}$ 5.0	$J_{2,3}$ 3.5	$J_{2,3}$ 9.0
		$J_{2,4b}$ 1.0					
H-3	5.46 (ddd)	4.92 (ddd)	4.26 (d)	4.16 (d)	3.92 (dd)	3.60 (dd)	3.37
	$J_{3,4a}$ 7.0	$J_{3,4a}$ 11.0	$J_{3,4}$ 8.0	$J_{3,4}$ 7.5	$J_{3,4}$ 9.5	$J_{3,4}$ 9.5	n.a.
	$J_{3,4b}$ 12.5	$J_{3,4b}$ 5.5					
H-4a	2.40 (ddd)	1.84 (ddd)	3.50 (dd)	3.49 (dd)	3.52 (t)	3.54 (t)	3.28
	$J_{4a,4b}$ 12.5	$J_{4a,4b}$ 12.5	$J_{4,5}$ 9.0	$J_{4,5}$ 9.0	$J_{4,5}$ 9.5	$J_{4,5}$ 9.5	n.a.
	$J_{4a,5}$ 2.0	$J_{4a,5}$ 11.0					
H-4b	2.06 (ddd)	1.79 (dddd)	-	-	-	-	-
	$J_{4b,5}$ 11.0	$J_{4b,5}$ 3.0					
H-5	4.15	3.66 (dddd)	3.46 (ddd)	3.32 (ddd)	3.33 (ddd)	3.24 (ddd)	3.28
	n.a.	$J_{5,6a}$ 5.0	$J_{5,6a}$ 2.0	$J_{5,6a}$ 2.5	$J_{5,6a}$ 2.5	$J_{5,6a}$ 2.0	n.a.
		$J_{5,6b}$ 5.0	$J_{5,6b}$ 6.0	$J_{5,6b}$ 6.5	$J_{5,6b}$ 6.0	$J_{5,6b}$ 6.5	
H-6a	4.21 (dd)	4.11	3.84 (dd)	3.83 (dd)	3.84 (dd)	3.84 (dd)	3.81
	$J_{5,6a}$ 4.5	n.a.	$J_{6a,6b}$ 12.5	$J_{6a,6b}$ 12.0	$J_{6a,6b}$ 12.5	$J_{6a,6b}$ 12.0	n.a.
	$J_{6a,6b}$ 11.5						
H-6b	4.15	4.11	3.66 (dd)	3.65 (dd)	3.69 (dd)	3.64 (dd)	3.62
	n.a.	n.a.					n.a.

a. δ-values (ppm) and coupling constants (*J*, Hz) for compounds **3-9** (500 MHz); n.a. means not possible to measure the coupling constants.

b. $CDCl_3$ (δ 7.27 ppm).

c. D_2O (acetone used as internal reference at δ 2.17 ppm).

d. MeOH-d_4 (δ 3.31 ppm).

crystallised (162 mg, 39%, mp 85–88 °C). Recrystallisation from Et_2O afforded an analytical sample: mp 88.5–89.5 °C; $[\alpha]_D$ –18.5° (*c* 1.1, $CHCl_3$).

Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.15; H, 6.12.

3,6-Di-*O*-acetyl-1,5-anhydro-4-deoxy-D-*lyxo*-hexitol (4). The unsaturated ketone **2** (189 mg, 0.828 mmol) was dissolved in EtOAc (20 mL) and hydrogenated at 3 x 10^6 Pa in the presence of 5% Pd/C (20 mg) overnight. The catalyst was filtered off, the filtrate dried ($MgSO_4$) and concentrated to a syrup (173 mg). Chromatography (4 g silica, eluted with hexane-EtOAc, 1:1) yielded **4** as a syrup (94 mg, 49%). An analytical sample was obtained by chromatography: $[\alpha]_D$ –34.1° (*c* 1.1, $CHCl_3$). HRMS: Calcd for $C_{10}H_{16}O_6$: 232.1025; found: 233.1031 ($M+H^+$).

1,5-Anhydro-D-fructose oxime (5). Hydroxylamine hydrochloride (246 mg, 3.54 mmol) and KOH pellets (85%, 205 mg, 3.11 mmol) in EtOH (15 mL) was stirred for 1 h. The salts were filtered off and washed with EtOH (15 mL). The filtrate was cooled to 0 °C under N_2 atmosphere and 1,5-anhydro-D-fructose (**1**) (572 mg, 3.5 mmol) was added. The suspension was stirred vigorously at ambient temperature overnight. Filtration afforded **5** as crystals (415 mg, 66%, mp 167–170 °C (decomp.)). Two recrystallisations from H_2O yielded an analytical sample: mp 179–181 °C (decomp.); $[\alpha]_D$ –46.2° (*c* 1.2, H_2O); (lit.[1] mp 178–180 °C; $[\alpha]_D$ –43° (*c* 0.3, H_2O); lit.[16] mp 155–157 °C; $[\alpha]_D$ –46.2° (*c* 1.2, H_2O)).

Anal. Calcd for $C_6H_{11}NO_5$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.66; H, 6.28; N, 7.76.

1,5-Anhydro-D-fructose *O*-benzyloxime (6). *O*-Benzylhydroxylamine hydrochloride (1.0 g, 6.3 mmol) and KOH pellets (85%, 350 mg, 5.3 mmol) in EtOH (15 mL) were stirred for 1 h. The salts were filtered off and washed with EtOH (15 mL). The filtrate was cooled to 0 °C and 1,5-anhydro-D-fructose (**1**) (1.0 g, 6.3 mmol) was added as a solid under an argon atmosphere. The mixture was stirred at ambient temperature overnight. Concentration gave **6** as a crude residue, which crystallised by addition of Et_2O (1.5 g, 91%, mp 98–100 °C). Two recrystallisations from H_2O afforded an analytical sample: mp 104–105 °C; $[\alpha]_D$ –18.9° (*c* 1.2, THF).

Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.23; H, 6.41; N, 5.01.

2-Amino-1,5-anhydro-2-deoxy-D-mannitol hydrochloride (7). To a suspension of 1,5-anhydro-D-fructose oxime (**5**) (540 mg, 3.1 mmol) in MeOH (30 mL) a mixture of MeOH (10 mL), AcCl (0.43 mL, 6.1 mmol) and 5% Pd/C (50 mg) was added. Hydrogenation at 55 x 10^5 Pa was performed overnight followed by addition of H_2O (30 mL) and removal of the catalyst by filtration. Concentration of the filtrate afforded **7** as a crude product (590 mg, 97%), that crystallised upon addition of EtOH (0.436 g, 72%, mp >260 °C). Recrystallisation from EtOH-H_2O afforded an analytical sample: mp >260 °C, lit.[17] 291–293 °C (dec.); $[\alpha]_D$ –38.9° (*c* 1.1, H_2O), lit.[17] –40°.

Anal. Calcd for $C_6H_{14}NO_4Cl$: C, 36.10; H, 7.07; Cl, 17.36; N, 7.02. Found: C, 35.97; H, 6.99; Cl, 17.51; N, 6.64.

1,5-Anhydro-D-mannitol (8). 1,5-Anhydro-D-fructose (**1**) (1.0 g, 6.2 mmol) was dissolved in H_2O (30 mL) and hydrogenated at 50 °C under 20 x 10^5 Pa pressure in the presence of 5% Pd/C (100 mg) for 5 days. Filtration and concentration left a syrup which was co-evaporated with toluene three times. The crude residue (1.0 g, quantitative) was shown by ^{13}C NMR to consist of 1,5-anhydro-D-mannitol (**8**) and the C-2 epimer, 1,5-anhydro-D-glucitol (**9**) in a 4:1 ratio. Upon addition of EtOH, **8** crystallised (583 mg, 58%, mp 143–147 °C). Three repeated recrystallisations from EtOH afforded an analytical sample: mp 152–154 °C, lit.[18] 155–157 °C (cor.); $[\alpha]_D$ –50.0° (*c* 1.0, H_2O), lit.[18] –50°.

Anal. Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 44.02; H, 7.41.

1,5-Anhydro-D-glucitol (9). 1,5-Anhydro-D-fructose (**1**) (1.1 g, 6.6 mmol) was dissolved in H_2O (30 mL) and left for 24 h. The solution was cooled to 0 °C and $NaBH_4$ (383 mg, 10.1 mmol) was added and the mixture stirred for 1 h at 0 °C, followed by 1 h stirring at ambient temperature. The solution was neutralised with ion exchange resin (Amberlite IR-120, H^+), concentrated and co-concentrated with 1% HCl (MeOH) three times. The residue was dissolved in EtOH and filtered while hot, followed by concentration to give a syrup (1.0 g, 95%) which was shown from ^{13}C NMR spectral data to consist of 1,5-anhydro-D-glucitol (**9**) and 1,5-anhydro-D-mannitol (**8**) in a 4:1 ratio. Upon addition of EtOH, **9** crystallised (0.651 g, 60%, mp 110–114 °C). Three recrystallisations from EtOH afforded an analytical sample: mp 138–139 °C, lit.[19] 141–142 °C; $[\alpha]_D$ +42.5° (*c* 1.1, H_2O), lit.[19] +42.5°.

Anal. Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 44.20; H, 7.31.

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