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Note

Dimeric structures of 1,5-anhydro-D-fructose[1]

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Abstract

Upon treatment with acetic anhydride-pyridine, 1,5-anhydro-D-fructose gave the enolone 1,5-anhydro-4-deoxy-D-*glycero*-hex-3-eno-pyranose-2-ulose as a product of elimination, which is thus available in an overall yield of 25% from D-glucose. During this reaction, acetylated dimers of 1,5-anhydro-D-fructose were formed in a side reaction, whereas these were the only products when acidic acetylation conditions were applied. The acetylated dimers were isolated and served for an unequivocal structural assignment of dimeric forms of 1,5-anhydro-D-fructose **1** by NOESY experiments. Whereas anhydroketose **1** forms dimers in Me_2SO and pyridine, its C-4 epimer, 1,5-anhydro-D-tagatose, did not form dimeric structures, neither in non aqueous nor in aqueous solvents. © 1998 Elsevier Science Ltd. All rights reserved

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1,5-Anhydro-D-fructose (**1**, Scheme 1) is of interest as a precursor of antibiotics [1–4] and for various chemical modifications. Synthesis of **1** has been accomplished by enzymatic conversion [1,5–10] or chemical multi-step reactions [11,12]. We obtained **1** by enzymatic oxidation of the corresponding 1,5-anhydro-D-hexitol with pyranose-2-oxidase from the fungus *Peniophora gigantea* [13,14], in a procedure that will be published elsewhere [15]. We were now able to convert **1** into the enolone **2** by treatment with acetic anhydride in pyridine. The enolone **2**, a synthetically interesting product that might be useful in a variety of reactions [16–19], is thus available in a chemoenzymatic approach in 25% yield and four steps from D-glucose.

Besides the enolone **2**, dimeric forms of acetylated 1,5-anhydro-D-fructose **3** (24%) and **4** (12%) were obtained when basic reaction conditions were applied. Upon acidic acetylation conditions ($HClO_4$), elimination products were not observed, but solely formation of dimers **3** and **4**. The compounds were isolated and served for an unequivocal structural assignment of dimeric forms of 1,5-anhydro-D-fructose (**1**) by NOE spectroscopy.

In aqueous solution, **1** exclusively exists in a hydrated pyranoid form **1a** [20]. In other solvents the same compound was reported to form dimers but the NMR spectra were not assigned due to their complexity [21]. We found that solutions of anhydroketose **1** in Me_2SO-d_6 contained the non hydrated anhydroketose **1b** together with two dimeric forms **5** and **6** in 15 and 9% proportions, respectively. In pyridine-d_5 dimeric structures predominated, **5**, **6**, and **1b** were found in 50, 10, and 40% ratios, respectively. Although the ^1H and ^{13}C

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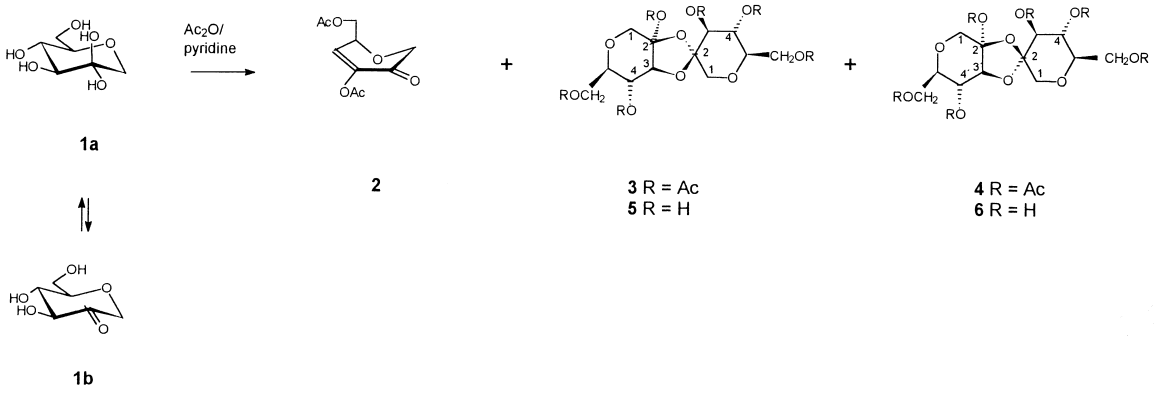


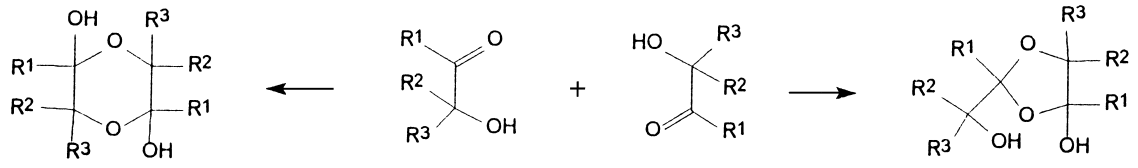
Scheme 1.

NMR spectra of dimers **5** and **6**, as well as **3** and **4** were completely assigned, an unequivocal structural assignment of the dimers was not possible from these data. We therefore performed NOESY experiments on the isolated acetylated dimers **3** and **4**.

Dimeric structures of dicarbonyl carbohydrates have been assigned in the case of 1,6-anhydro-hexosuloses [22–24] and methyl ketosides [25] and the formation of dimers under acidic or thermal conditions has been reported for ketoaldoses [26] as well as ketoses [27–30]. The dimers of α-hydroxy aldehydes and ketones may theoretically be formed as symmetrical or unsymmetrical 1,4-dioxane or dioxolane compounds (Scheme 2).

The NMR spectra of **3** and **4**, as well as **5** and **6**, clearly show evidence of the existence of asymmetric dimers. The C-2′ atoms in both acetylated and non acetylated dimers resonate around 100 ppm, which indicates a 2,6-cyclised pyranoid anhydroketose and is in agreement with the resonances found for the spiroketal function in dihexulose dianhydrides [28–31]. The C-2 atom of the other ring shows a relative downfield shift at around 108–110 ppm and indicates a quarternary carbon in a dioxolane type ring. The resonances for C-3 and C-3′ of both rings show differences of up to 12 ppm. This accounts for the fact that O-3′ is involved in the dioxolane ring closure. Similar differences in chemical shifts are observed for H-3 and H-3′ in the ^{1}H NMR spectra. The coupling constants in these spectra show a perfect $^4C_1$ chair for the right ring bearing the spiroketal group, whereas the coupling constants for the primed ring ($J_{3',4'}$ 5.8 and 6.7 Hz in **5** and **6**, respectively; $J_{3,'4'}$ 6.1 and 4.8 Hz in **3** and **4**; as well as $J_{4',5'}$ 6.3 Hz in **4**) indicate a noticeably flattened chair for this ring, a fact that has been previously observed in crystal structures of pyranoses bearing annelated five-membered rings [32,33]. From these findings it could be concluded, that the two distinct dimers were asymmetric structures with a five-membered central ring and one spiroketal function and the four structures A–D had to be considered. The dioxolane ring may bear a *trans*-configuration in positions 2′ and 3′ as in A and B, or a *cis*-relationship as in C and D (Fig. 1).

The data so far accumulated for **4** and **6** did not allow discrimination between the four possible structures A–D; we therefore performed NOE spectroscopy of the isolated acetylated dimers **3** and **4**. The NOESY spectra revealed interglycosidic contacts between H-1e–H-3′ (11%) in **3** and between H-1e–H-4′ (31%) in **4**. The H-1e–H-4′ contact in **4** clearly confirmed the existence of structure D for the minor isomer **4** (1.8:1 in Me_2SO and 5:1 in pyridine for **3** and **4**, respectively).



Scheme 2.

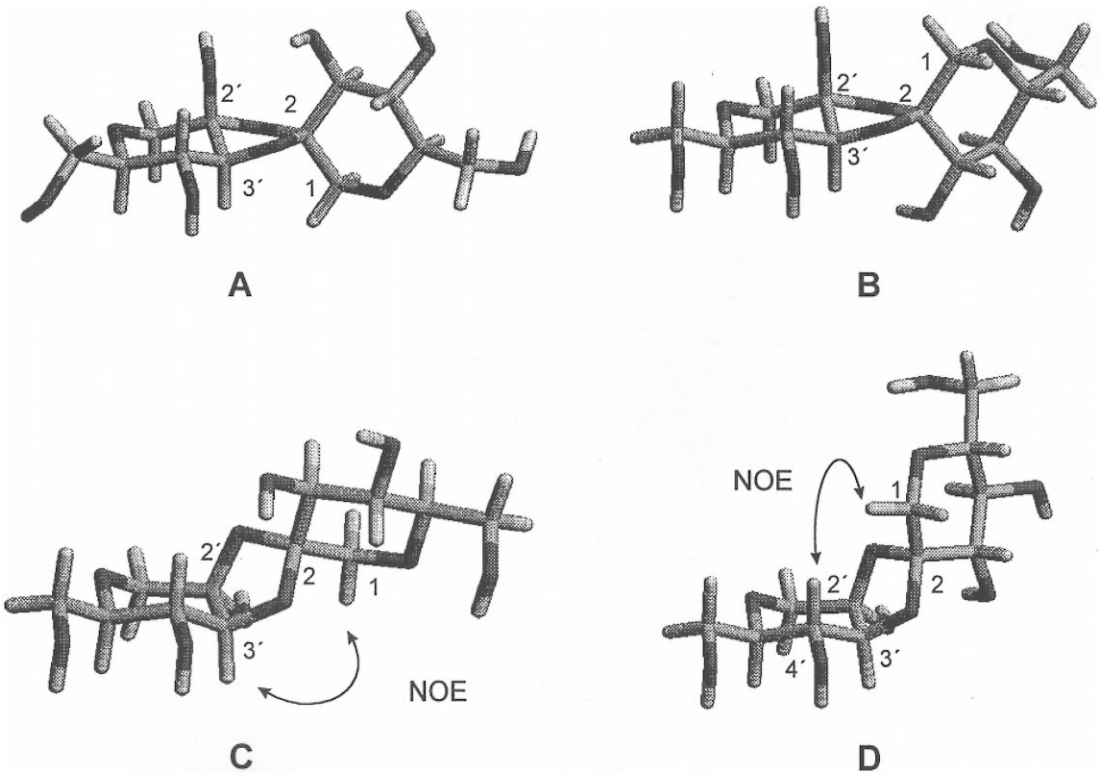
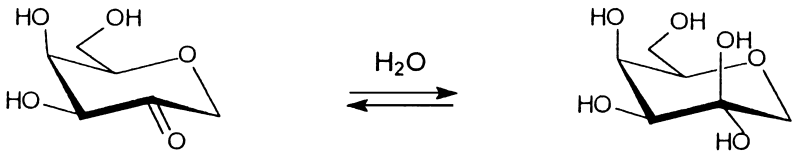


Fig. 1. Energy minimised (SYBYL) structures of possible asymmetric dimers of 1,5-anhydro-D-fructose (**1**).

Although the existence of a NOE H-1e–H-3′ contact in **3** could be attributed to both isomers A and C, the relative size of the contact supported structure C. The relatively small contact observed fits better with the estimated distance H-1e–H-3′ of 3.5 Å in C than of 2.5 Å in A, when compared to the size of the other contacts in **3** or to the relative contact H-1e–H-4′ of 31% **4** with an estimated distance H-1e–H-4′ of 2.3 Å. The relative values of the numerous intra ring NOE contacts are well in agreement with these structures and with the finding that the right pyranose ring is in a perfect $^4C_1$ chair conformation in both dimers **3** and **4**, whereas the left ring adopts a slightly distorted chair conformation. Although the structural assignment of the dimers was performed solely on the isolated acetylated derivatives, we believe that the acetylated forms **3** and **4** are derivatives of the free dimers **5** and **6** in non aqueous solutions. This is indicated by comparable ratios of free **5** and **6** (1.8:1 in Me_2SO; 5:1 in pyridine) and the acetylated dimers **3** and **4** (2:1) and the very comparable but striking differences in chemical shifts of C-4–C-4′ and H-4–H-4′ in dimers **3** and **5**, but not in **4** and **6**. The two dimeric forms of 1,5-anhydro-D-fructose formed under acetylating conditions are thus both *cis*-configured dioxolane-type dimers that differ in the orientation of the spiroketal function C-2.

Recently, the NMR data for the C-4 epimer of **1**, 1,5-anhydro-D-tagatose (**8**, Scheme 3) could not be determined by Barili et al. [34] due to the complexity of the spectra. This led the authors to



8a **8b**

Scheme 3.

assume the formation of dimeric or other structures in solution, which is also supported by our finding that the epimer **1** forms 60% of dimeric structures in pyridine. We therefore investigated the formation of dimers of this compound. 1,5-Anhydro-D-tagatose (**8**) was obtained by the same enzymatic oxidation [13,14] and it was found that in aqueous solutions, both the free ketopyranose **8a** and the hydrated pyranose **8b** were present in a 7:3 ratio. Astonishingly, neither in Me_2SO-d_6 nor in pyridine-d_5 were dimeric structures detectable. Consequently 1,5-anhydro-D-tagatose (**8**) exclusively yields the elimination product **2** under acetylating conditions, which might be rationalised by the fact that the *trans*-diaxial arrangement of H-3 and AcO-4 facilitates a β-elimination through a E_2 mechanism.

1. Experimental

General methods.—The reactions were monitored by TLC on silica gel 60 F_{254} (E. Merck) and the spots were detected by UV absorption and staining with sulphuric acid. For column chromatography silica gel 60 (E. Merck) was used. Optical rotations were determined with a Perkin-Elmer model 241 MC. Mass spectra were obtained on a MAT 212 from Finnigan (70 eV, He gas support) using chemical ionisation. NMR spectra were recorded on a Bruker AMX 500 spectrometer at 500.13 MHz for ^1H and 125.76 MHz for ^{13}C at 300 K. Chemical shifts are referenced to internal acetone ($\delta = 2.030$ and 30.50) for D_2O as solvent; in $CDCl_3$ to $\delta = 7.270$ and 77.00 and in Me_2SO-d_6 to $\delta = 2.490$ and 39.50 ppm for these solvents, respectively. 1D, as well as 2D HMQC and 2D NOESY spectra were recorded using the standard Bruker software. For the NOESY spectra mixing times of 300 and 900 ms were used. A baseline correction was applied in both dimensions and the volume integration is given relative to the diagonal peak of H-3.

3,6-Di-O-*acetyl-1,5-anhydro-4-deoxy*-D-glycero-*hex-3-enopyranose-2-ulose* (**2**), *[(2*R,*3*R,*4*S,*5*S)-*3,4-diacetoxy-2-acetoxymethyl-tetrahydropyran]-5*-spiro-*5′-[(1′*R,*2′*R,*3′*S,*7′*S)-*2′,7′-diacetoxy-1′-acetoxymethyl-4′,6′,9′-trioxabicyclo[4,3,0]nonane]* (**3**), *and [(2*R,*3*R,*4*S,*5*S)-*3,4-diacetoxy-2-acetoxymethyl-tetrahydropyran]-5*-spiro-*5′-[(1′*R,*2′*R,*3′*S, *7′*R)-*2′,7′-diacetoxy-1′-acetoxymethyl-4′,6′,9′-trioxabicyclo[4,3,0]nonane]* (**4**).—A soln of 35 mg (0.21 mmol) of dry **1** in 2 mL of pyridine and 0.5 mL of Ac_2O was kept at 5 °C overnight. After addition of 5 mL of water the solution was extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated several times with toluene. Column chromatography using 1:2 AcOEt–petroleum ether for elution first yielded 21 mg (45%) of syrupy **2**: $[\alpha]_D^{20} = -17.7°$ (*c* 0.34 in CH_2Cl_2); MS: *m*/*z* 229 (48) $[M]^+$, 187 (10) $[M–CH_2CO]^+$, 169 (100%) $[M–HOAc]^+$, 127 (22); ^1H NMR and ^{13}C NMR ($CDCl_3$) signals of the protecting groups: δ 2.128, 2.265 (6 H, CH_3CO); 20.25, 20.80 (CH_3CO), 168.05, 170.66 (CH_3CO); other NMR data see Tables 1 and 2. Anal. Calcd for $C_{10}H_{12}O_6$ (228.2): C, 52.63; H, 5.30. Found C, 52.54; H, 5.43.

Further elution with 2:1 EtOAc–petroleum ether gave 21 mg (36%) of slowly crystallising syrup as a

Table 1
^{13}C NMR chemical shifts δ (ppm)

	C-1–C-1'	C-2–C-2'	C-3–C-3'	C-4–C-4'	C-5–C-5'	C-7–C-7'
8[b]	72.38	208.49	76.02	72.75	78.74	61.19
9[b]	72.61	92.40	71.86	69.41	80.02	61.45
1b[c]	72.10	204.98	79.13	73.07	81.25	60.97
5[c]	69.38	107.63	73.87	69.53	81.45	61.41
	71.17	99.87	88.57	68.21	80.31	61.79
6[c]	68.62	108.53	74.51	69.83[a]	81.51[a]	61.05[a]
	71.71	100.37	87.19	70.02[a]	80.14[a]	61.17[a]
2[d]	71.43	187.65	132.75	143.81	72.62	64.39
3[d]	71.47	108.53	70.96	68.56	76.86[a]	62.72[a]
	69.15	105.25	82.81	70.08	75.11[a]	63.27[a]
4[d]	71.92	109.41	73.32	68.67	76.46	62.55[a]
	69.22	104.63	82.54	68.67	75.58	63.25[a]

Atom numbering according to carbohydrate nomenclature, see also Scheme 1.
[a] Signal assignment may be inverted.
[b] In D_2O.
[c] In Me_2SO-d_6.
[d] In $CDCl_3$.

Table 2
^{1}H NMR chemical shifts δ (ppm) and coupling constants (Hz)

	H-1e–H-1′e	$J_{1e,1a}$	H-1a–H-1′a	H-3–H-3′	$J_{3,4}$	H-4–H-4′	$J_{4,5}$	H-5–H-5′	$J_{5,6a}$	$J_{5,6b}$	H-6a–H-6′a	$J_{6a,6b}$	H-6b–H-6′b
8a[b,e]	4.019[a]	15.0	3.904[a]	4.417	3.9	4.169	0.6	3.896	6.7	5.6	3.571	n.d.	n.d.
8b[b]	3.573[a]	11.9	3.205[a]	3.520	3.8	3.702	1.1	3.403	7.9	4.2	3.550	11.7	3.503
1b[c]	4.062[a]	14.1	3.859[a]	4.067	9.0	3.349	n.d.	3.472	4.4	AB	3.708	13.1	3.470
5[c]	3.889[a]	13.1	3.428[a]	3.309	9.9	3.200	9.0	3.033	n.d.	n.d.	3.643	12.5	3.377
	3.949[a]	11.7	3.139[a]	3.810	5.8	3.863	11.7	3.124	~8	n.d.	3.616	12.5	3.343
6[c]	3.855[a]	11.0	3.368[a]	3.398	9.6	3.168	9.0	~3.03	n.d.	n.d.	3.640	~12	3.392
	3.572[a]	11.6	3.388[a]	3.818	6.7	3.114	~12	3.040	n.d.	n.d.	3.617	~12	3.389
2[d,f]	4.462[a]	16.5	4.259[a]	—	—	6.608	2.3	4.803	6.1	4.3	4.421	11.8	4.251
3[d]	3.980	12.1	3.510	5.334	10.0	5.146	10.0	3.675	6.0	3.1	4.208	12.3	4.133
	4.550	12.0	3.896	4.730	6.1	5.303	9.1	3.675	AB	AB	4.150	AB	4.150
4[d]	4.048	12.0	3.562	5.243	9.7	5.079	9.8	3.675	2.6	5.5	4.214	12.5	4.162
	4.755	12.5	3.806	4.425	4.8	4.950	6.3	3.727	3.8	6.4	4.198	11.8	4.110

	OH-2	$J_{3,OH-3}$	OH-4	$J_{4,OH-4}$	OH-6	$J_{6,OH-6}$	OH-3′	$J_{3',OH-3'}$	OH-4′	$J_{4',OH-4'}$	OH-6′	$J_{6',OH-6'}$
1b	5.404[g]	5.5	5.506	5.7	4.632	5.3	—	—	—	—	—	—
5	6.484	—	5.065	5.6	4.498	5.5	4.670	5.4	4.903	5.5	4.486	6.3
6	6.866	—	5.523	6.1	4.570[a]	5.9	n.d.	n.d.	5.186	5.6	4.512[a]	5.8

Atom numbering according to carbohydrate nomenclature, see also Scheme 1; n.d., not determined.
[a] Signal assignment may be inverted.
[b] In D_2O.
[c] In Me_2SO-d_6.
[d] In $CDCl_3$.
[e] $J_{1a,5} = 1.8$ Hz.
[f] $J_{1e,3} = 1.0$ Hz.
[g] OH-3.

mixture of **3** and **4** in the ratio 2:1 (NMR): mp 60–62 °C; MS: 517 (38) $[M–HOAc]^+$, 457 (14) $[M–2·HOAc]^+$, 397 (3) $[M–3·HOAc]^+$, 337 (4) $[M–4·HOAc]^+$, 277 (2) $[M–5·HOAc]^+$, 229 (100) [M/2 + 1–HOAc]. Anal. Calcd for $C_{24}H_{32}O_{16}$ (576.5): C, 50.00; H, 5.59. Found C, 50.13; H, 5.41.

For structural assignment using NOE spectroscopy an analytical sample was separated by HPLC on LiChrosorb Si 60 (E. Merck, 1:1 EtOAc–petroleum ether). ^{1}H NMR and ^{13}C NMR signals of the protecting groups: **3**: δ 2.025, 2.046, 2.059, 2.094, 2.116, 2.191 (18 H, C*H*$_3$CO); 20.52, 20.62, 20.73, 20.75, 20.78, 21.67 (*C*H$_3$CO); 169.04, 169.16, 169.24, 169.99, 170.53, 170.64 (CH$_3$*C*O). **4**: δ 2.024, 2.076, 2.095, 2.098, 2.100, 2.120 (18 H, C*H*$_3$CO, 20.61, 20.73 (2×), 20.79, 20.89, 21.66 (*C*H$_3$CO), 168.87, 169.28, 169.37, 169.71, 170.57, 170.73 (CH$_3$*C*O). For other NMR data see Tables 1 and 2. NOE contacts (% relative to the effect H-1a–H-1e): **3**: H-1a–H-3 (29), H-1a–H-5 (21), H-4–H-5 (26), H-4–H-6a (16), H-4–H-6b (28), H-1e–H-3′ (11), H-1′a–H-1′e (119), H-1′a–H-3′ (5), H-1′a–H-5′ (56), H-3′–H-4′ (55), H-3′–H-5′ (30), H-4′–H-6′a (63). **4**: H-1a–H-3 (23), H-1a–H-5 (29), H-3–H-4 (18), H-4–H-5 (66), H-4–H-6a (17), H-4–H-6b (28), H-1e–H-4′ (31), H-1′a–H-1′e (107), H-1′a–H-3′ (7), H-1′a–H-5′ (29), H-3′–H-4′ (23), H-3′–H-5′ (18), H-4′–H-5′ (65), H-4′–H-6′a (17), H-4′–H-6′b (28).

2 *from acetylation of 1,5-anhydro-*D*-tagatose* (**8**).—A total of 19 mg (0.12 mmol) of **8** were treated with Ac_2O-pyridine as described above. Separation by column chromatography (1:2 EtOAc–petroleum ether) yielded 17 mg (64%) of a colourless syrup that was identical to compound **2**.

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