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A convenient access to the 1,5-anhydro forms of D-tagatose, L-rhamnulose and D-xylulose via 2-hydroxyglycal esters ☆

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ABSTRACT

Zemplén methanolysis or a three-step protocol comprising hydroxylaminolysis, de-O-acetylation and deoximination smoothly and efficiently convert the benzoylated 2-hydroxy-D-glycals of D-galactose, L-rhamnose and D-xylose into their configurationally related 1,5-anhydro-ketoses, thereby providing convenient access to the 1,5-anhydro forms of D-tagatose, L-rhamnulose and D-xylulose. Invariably obtained as amorphous solids, they are best characterized through their highly crystalline oximes.

1. Introduction

Potential applications of 1,5-anhydro-D-fructose **1** as a powerful antioxidant,[2,3] an antimicrobial agent,[2,3] a food additive[3] or a pharmaceutical[4] have generated the elaboration of a series of chemical and enzymatic syntheses, the most convenient being the α-1,4-glucan lyase-induced degradation of starch,[5] and the Zemplén methanolysis of tetra-*O*-acetyl-2-hydroxy-D-glucal.[1] Of other 1,5-anhydro-ketoses, which are likely to have similar application profiles, only 1,5-anhydro-D-tagatose **2** has become known, either through a laborious seven-step chemical procedure starting from D-galactose,[6] or by bacterial oxidation of 1,5-anhydro-D-galactitol,[7] whose acquisition from D-galactose requires four steps.

Relying on the methodology developed for the obtention of 1,5-anhydro-D-fructose,[1] we here describe convenient procedures for the conversion of D-galactose, L-rhamnose and D-xylose into the 1,5-anhydro derivatives of D-tagatose **2**, L-rhamnulose **3** and D-xylulose **4**, respectively.

2. Results and discussion

2.1. 1,5-Anhydro-D-tagatose

The methodology recently advanced for the straightforward liberation of 1,5-anhydro-D-fructose from 2-hydroxy-D-glucal esters,[1] (direct Zemplén methanolysis or a three-step protocol involving enol ester hydroxylaminolysis, de-O-acylation and deoximation) could readily be applied to the D-*galacto* analogue **5** with only minor experimental adaptations: Exposure to hydroxylamine hydrochloride in pyridine at ambient temperature smoothly converted **5** into the *E*-oxime **6** (82%), readily deprotectable by Zemplén methanolysis to **7** (Scheme 1), both oximes feature useful properties such as high crystallinity and ease of isolation. Their deoximation with acetaldehyde/HCl either afforded 1,5-anhydro-D-tagatose **2** or its triacetate **8** in excellent yields, yet as revealed by ^{1}H and ^{13}C NMR data, both accumulated as mixtures of the keto and 2,2-dihydroxy (hydrate) forms in ratios varying between 5:2 and 2:1 in favour of the monohydrates. This tendency towards elaboration of the monohydrate forms—in the case of **2** ⇌ **2**·H_2O already previously observed by Freimund and Köpper[7]—is in distinct contrast to that of the 4-epimeric 1,5-anhydro-D-*fructo* compounds: the corresponding ulose triacetate, analogously prepared by hydroxylaminolysis of the 2-hydroxy-D-glucal ester and subsequent deoximation, was obtained in crystalline form (89%) as the unhydrated ketose,[1] whilst 1,5-anhydro-D-fructose **1** fully adopts the 2,2-dihydroxy (hydrate) form in aqueous solution.

1 (D-*fructo*) **2** (D-*tagato*)

3 (L-*rhamnulo*) **4** (D-*xylulo*)

In the acetylated ulose **8**, β-elimination of acetic acid is facilitated by the *trans*-diaxial disposition of H-3 and 4-OAc; thus conversion to the enolone ester **11** already occurred on longer contact

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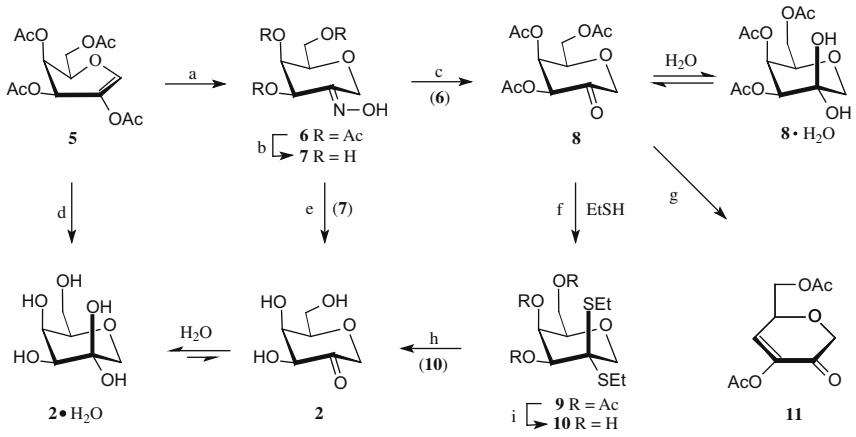


Scheme 1. Reactions and conditions: (a) $NH_2OH{\cdot}HCl$/pyridine, 15 h, rt, 82%; (b) NaOMe/MeOH, 20 min, rt, 78%; (c) acetaldehyde/HCl in MeCN, 6 h, rt, 95%; (d) NaOMe/MeOH, 2 h at −15 °C→rt, 84%; (e) acetaldehyde/HCl in MeCN, 5 h, rt, 83%; (f) EtSH (BF_3, 15 min, rt, 61%; (g) NaOAc/acetone, 1 h, rt, 91%; (h) $CdCO_3/HgCl_2$ in water, 30 min, rt, 69%; (i) NaOMe/MeOH, 3 h, 0 °C, 87%.

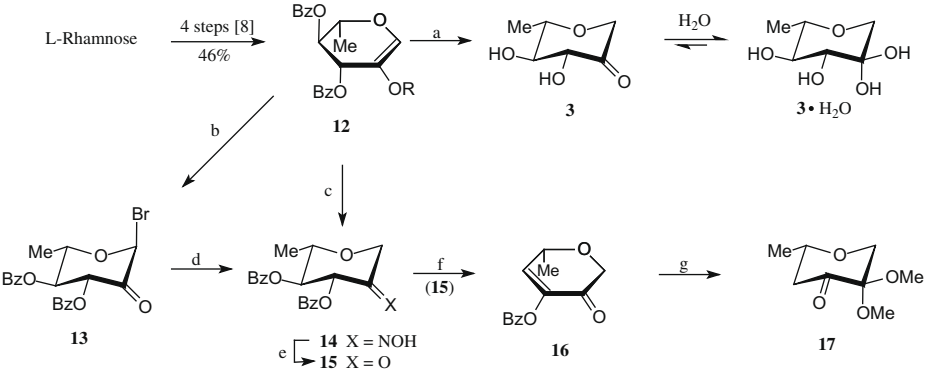
with silica gel or, for preparative purposes, by briefly stirring with sodium acetate in acetone. Mercaptalization was readily effected by exposure to ethanethiol/HCl to provide **9**, which could also be converted into 1,5-anhydro-D-tagatose **2** by Zemplén methanolysis to **10** and subsequent desulfurization. By far the most simple generation of 1,5-anhydro-D-tagatose, however, proved to be the direct Zemplén methanolysis of the 2-acetoxygalactal triacetate **5** which, when performed at low temperature, proceeded without β-elimination, obviously due to the formation of the monomethanolate **8**·MeOH as the first intermediate rather than the ketose **8** which under the slightly basic Zemplén conditions would readily undergo β-elimination to enolone **11**.

2.2. 1,5-Anhydro-L-rhamnulose

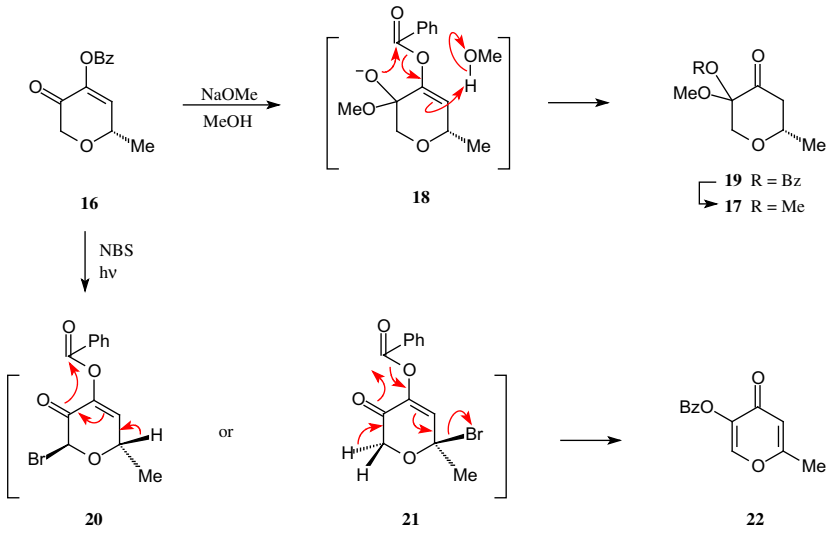
Being readily accessible in a four-step, large scale-adaptable protocol from L-rhamnose,[8] the 2-benzoyloxy-L-rhamnal dibenzoate **12** was similarly subjected to Zemplén methanolysis which proved to be somewhat capricious due to its low solubility in methanol and, hence, comparatively long contact to the basic conditions (NaOMe/MeOH). However, when working at low temperature (−10→0 °C) in high dilution and short-reaction times (3–5 min), the parent sugar, 1,5-anhydro-D-rhamnulose **3** could be released without appreciable formation (TLC) of side products; it was characterized as an amorphous solid, which in aqueous solution adopted the 2,2-dihydroxylated (monohydrate) form **3**·H_2O.

The well-crystallizing dibenzoate of 1,5-anhydro-L-rhamnulose **15** could be procured in either one of two ways: through hydroxylaminolysis of the L-rhamnal ester **12** and subsequent transoximation of the oxime **14**→**15**, or, alternatively, by tributyltin hydride-promoted debromination of the rhamnosulosyl bromide **13**. Not unexpectedly, β-elimination of benzoic acid in **15** was readily induced either by brief heating in pyridine or by stirring with sodium acetate in acetone to provide the single-stereogenic-centre dihydropyranone **16**, a versatile enantiopure six-carbon building block (Scheme 2).

Exposure of dihydropyranone **16** to Zemplén methanolysis did not liberate the respective 2,3-diketone (or enol forms thereof), but gave the 2-dimethyl acetal **17** in a uniform reaction, conceivably proceeding through addition of methoxide onto the carbonyl group and subsequent 4-*O*-→5-*O*-benzoyl migration (to the methyl acylal **18**) and replacement of the benzoyloxy group by OMe (**18**→**17**). Such a course receives some credence by the detection of **19** by ^{1}H NMR and TLC on brief methanolysis, and by the obtention of benzoyl-allomaltol **22** on the attempt to anomerically refunctionalize dihydropyranone **16** by photobromination with NBS (Scheme 3). As observed for the 6-benzoyloxymethyl analogue of **16**,[9] the bromine radical either enters the anomeric position next to the carbonyl group (→**20**) or the one vinologous thereto (→**21**), each being capable of elaborating the γ-pyrone system via benzoyl group shifts[10] (arrows in **20** and **21**, respectively).



Scheme 2. Reactions and conditions: (a) NaOMe/MeOH, −10→0 °C, 84%; (b) NBS/MeOH in CH_2Cl_2, 30 min, rt, 75%;[8] (c) NH_2OH/pyridine in EtOH, 5 d, rt, 86%; (d) Bu_3SnH/AIBN in toluene, 5 h, 90 °C, 71%; (e) acetaldehyde/HCl in MeCN, 15 h, rt, 82%; (f) pyridine in $CHCl_3$, 5 min reflux, 87%; (g) NaOMe/MeOH, 5 min, rt, 68%.

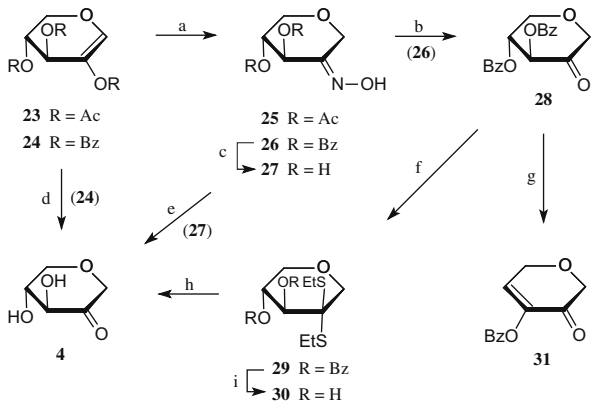


Scheme 3.

2.3. 1,5-Anhydro-D-xylulose

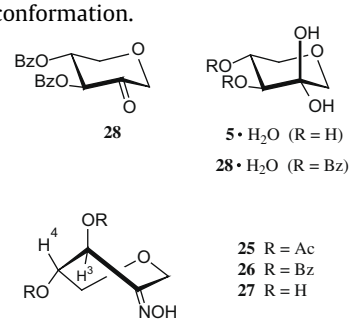
Application of the methodology developed for hydroxylaminolysis and Zemplén deacylation to the 2-hydroxy-D-xylal esters **23** and **24** proceeded in a straightforward manner providing the *E*-oximes **25**–**27**, the ulose dibenzoate **28**, as well as the respective diethyldithio acetals **29** and **30**, in crystalline form each and in satisfactory yields. The only peculiarity observed was that the form in which the ulose dibenzoate **28** accumulated on deoximation of **26** with acetaldehyde depended on the workup procedure: the ketose as such or its 2,2-diol (hydrate form), was separately isolable, and characterized by their distinctly different ^{1}H and ^{13}C NMR data, the former showing its C-2 resonance at 199.4, the hydrate at 91.7 ppm (Scheme 4).

Liberation of the unprotected 1,5-anhydro-D-xylulose **4** could be effected from the oxime **27** by transoximation, from the dithioacetal **30** by desulfurization and, preparatively most straightforward, by Zemplén methanolysis of the 2-acetoxy-D-xylal diacetate **23**. The resulting 1,5-anhydro-D-pentulose was characterized by NMR to be the monohydrate in aqueous solution, whilst in DMSO-d_6 or in pyridine-d_5, spectra turned out to be unusually complex indicating the presence of dimeric forms.



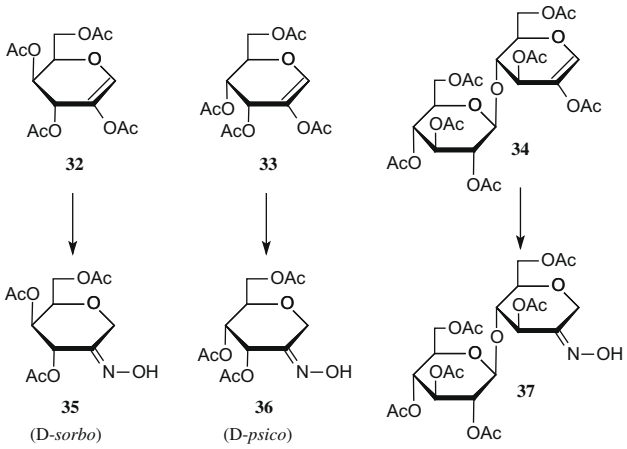
Scheme 4. Reactions and conditions: (a) $NH_2OH{\cdot}HCl$ in THF/acetate buffer pH 4.5, 20 h, rt or in pyridine 10 d, rt, 79% **25**, 75% **26**; (b) acetaldehyde/2 M HCl in MeCN, 18 h, rt, 92%; (c) NaOMe/MeOH, 1 h, rt, 63%; (d) NaOMe/MeOH, 2 h, −15 °C→rt, then H^+, 69%; (e) acetaldehyde/2 M HCl in MeCN, 5 h, rt, 78%; (f) EtSH/BF_3 in $CHCl_3$, 5 min, rt, 88%; (g) pyridine in $CHCl_3$, reflux, 10 min, 82%; (h) $CdCO_3/HgCl_2$ in water, 30 min, rt, 75%; (i) NaOMe/MeOH, 3 h, rt, 95%.

With respect to the conformations adopted by 1,5-anhydro-D-xylulose **4** and its derivatives **25**–**30**, ^{1}H NMR data—most notably their $J_{3,4}$ and $J_{4,5}$ values—reveal the uloses **4** and **28**, respectively, and their monohydrates to be in the $^{4}C_1$ conformation, whilst the couplings of the oximes **25**–**27** based on $J_{3,4}$ and $J_{4,5}$ values of 2.5–4 Hz are best interpreted by their adoption of the $^{0}S_2$ boat-twist or skew conformation.



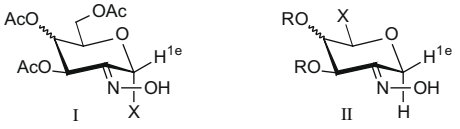
3. Conclusion

Simple protocols based on direct Zemplén methanolysis or on a three-step hydroxylaminolysis/deacylation/deoximation sequence have been elaborated to convert 2-hydroxyglycal esters of D-galactose, L-rhamnose and D-xylose into their configurationally related 1,5-anhydro-ketoses. The convenient access thereby provided to D-tagatose, L-rhamnulose and D-xylulose in their 1,5-anhydro forms now renders them available for evaluation of their application profiles, most notably of their potential antioxidant properties. Moreover, the methodologies developed for their acquisition are apt to be applicable to any other 2-hydroxyglycal ester, such as, for example, to the peracetates of 2-hydroxy-D–D-gulal **32**,[11] 2-hydroxy-D-allal **33**[11,12] and 2-hydroxy-cellobial **34**,[13] inasmuch as their enol ester hydroxylaminolysis smoothly provides the respective *E*-oximes **35**–**37** in crystalline form each. Thus, the low temperature Zemplén de-O-acetylations elaborated should similarly proceed in a straightforward manner furnishing, for example, 1,5-anhydro-D-sorbose from **32** and its D-*psico* analogue from **33**. In similar fashion, the readily accessible disaccharide-derived 2-hydroxyglycal esters **34**[13] and their benzoylated maltal, cellobial and lactal analogues[14] are to generate the underlying 4-*O*-glycosylated 1,5-anhydro-D-fructoses, should there be need for their availability.

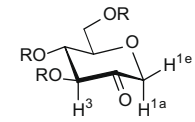


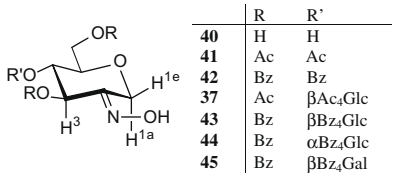
4. On the *E*-geometry of 1,5-anhydroketose oximes

Oximes of pyranoid 2-ketosugars, that is, α-D-glycosiduloses of type I, invariably assume the *Z* geometry with the oxime hydroxyl pointing in the direction of the anomeric centre, proof being derived from the significant deshielding of the equatorially oriented H-1 by the oxime hydroxyl which finds expression in an downfield shift of 0.9–1 ppm when going from the parent ketose to its oxime.[15] The *Z* assignments were in fact corroborated by several X-ray structures.[16]



Compounds differing from I only by the absence of an anomeric substituent, that is, 1,5-anhydroketoximes of type II, would similarly be anticipated to generally adopt the *E*-oxime geometry. This conjecture could readily be verified by comparison of ^{1}H and ^{13}C NMR data of the oximes and their parent 2-oxo analogues. As clearly evident from the juxtaposition of the D-*fructo*-configured oximes **37** and **40**–**45** to their 2-ulose counterparts **38** and **39**, the axially-oriented protons H-1 and H-3 show minimally changed chemical shifts (cf. Table 1), whereas the equatorial H-1 exhibits a distinct downward shift of 0.6 ppm when going from ulose to oxime. This clearly indicates that the oxime hydroxyl group is pointing towards the anomeric carbon rather than C-3, hence establishing the *E*-configuration for oximes **40**–**45**.





	R	R'
40	H	H
41	Ac	Ac
42	Bz	Bz
37	Ac	βAc4Glc
43	Bz	βBz4Glc
44	Bz	αBz4Glc
45	Bz	βBz4Gal

In the D-*tagato* and L-*rhamnulo* cases the respective downfield shifts for H-1e from ketose to oxime are even higher (0.8 ppm), which can only be rationalized by the *E*-geometry of the oximes. In the D-*xylulo* case **28** (Table 1, X = O) and **26** (X = NOH) there is a downfield shift of both, H-1e (0.23) and H-1a (0.27 ppm)—obviously due adaption of the $^{0}S_{2}$ boat-twist conformation of the pyranoid ring, wherein the oxime hydroxyl exerts its deshielding equally on either of the anomeric hydrogens.

The *E*-geometry of 1,5-anhydroketoximes can similarly be derived from the ^{13}C chemical shifts of the carbons vicinal to the carbonyl respectively, oximinocarbonyl group. As documented by vast literature data,[17,18] the ^{13}C resonances of the carbonyl and both vicinal carbons shift upfield on oxime formation, with the effect for the carbon on the same side as the N–OH group being greater than that for the other. In the case of 3-methyl cyclohexanone and its oxime these upfield shifts are 15.8 ppm for the oxime-OH deshielded carbon, yet still 9.6 ppm for the other (Fig. 1).

Figure 1. ^{13}C chemical shifts (ppm) of cyclohexanone versus those of its oxime.[17] The upfield shift for C-2 from ketone to oxime is significantly larger (15.8) than for C-6 (9.6 ppm).

Table 1
^{1}H NMR data for H-1 and the anomeric hydrogens of 1,5-anhydroketoses and acylated derivatives in comparison to those of their *E*-oximes

Configuration	1,5-Anhydroketoses X = O					1,5-Anhydroketose E-oximes X = N–OH					Ref.
		H-1e	H-1a	H-3	Solvent		H-1e	H-1a	H-3	Solvent	
D-*Fructo*	**1**[a]					**40**	5.03	3.89	4.25	D_2O	1
	38	4.25	4.09	5.41	$CDCl_3$	**41**	4.88	4.04	5.54	DMSO-d_6	1
	39	4.57	4.33	6.19	DMSO-d_6	**42**	5.17	4.22	6.02	$CDCl_3$	1
						37	4.91	4.03	6.80	DMSO-d_6	b
						43	4.96	[c]	6.13	$CDCl_3$	14
						44	4.90	[c]	6.12	$CDCl_3$	14
						45	4.91	[c]	5.89	$CDCl_3$	14
D-*Tagato*	**2**	4.04	3.92	4.45	D_2O	**7**	4.85	3.68	4.23	DMSO-d_6	b
	8	4.38	4.09	5.88	DMSO-d_6	**6**	5.01	3.94	5.76	DMSO-d_6	b
L-*Rhamnulo*	**15**	4.33	4.16	5.86	$CDCl_3$	**14**	5.12	4.00	5.94	$CDCl_3$	b
D-*Xylulo*	**4**[a]					**27**	4.48	4.04	3.90	DMSO-d_6	b
						25	4.52	4.28	5.36	$CDCl_3$	b
	28	4.44	4.21	6.13	Me_2CO-d_6	**26**	4.67	4.48	5.86	$CDCl_3$	b

[a] 1,5-Anhydro-D-fructose **1** and its D-xylulo analogue **4** adopt in water (D_2O) the 2,2-dihydroxy(hydrate) form, and hence are not suited for comparison.
[b] Data from this paper.
[c] Signal not resolved from glycosyl protons.

Table 2
^{13}C NMR data (ppm) for C-1 through C-3 of 1,5-anhydro-ketoses and acylated derivatives compared to those of their *E*-oximes

Configuration	1,5-Anhydroketoses					1,5-Anhydroketoximes				
	Compd.	C-1	C-2	C-3	Solvent	Compd.	C-1	C-2	C-3	Solvent
D-*Fructo*	**1**[a]	–	–	–		**40**	61.5	156.1	72.6	D_2O
D-*Fructo*	**38**	72.5	196.9	76.9	$CDCl_3$	**41**	62.9	150.6	69.7	DMSO-d_6
D-*Fructo*	**39**	72.5	197.9	77.5	DMSO-d_6	**42**	62.5	151.3	71.7	$CDCl_3$
D-*Tagato*	**2**	72.5	210.1	76.1	D_2O	**7**	59.4	153.7	69.5	DMSO-d_6
D-*xylulo*	**28**	67.5	199.4	77.3	Me_2CO-d_6	**26**	61.7	151.4	69.8	$CDCl_3$

[a] 1,5-Anhydro-D-fructose **1** forms dimers in the solid state and the hydrate in water, hence is unsuited for comparison.

Analogous shift differences are observed for the ^{13}C resonances of the four ketose/oxime examples listed in Table 2: in the D-*fructo* and D-*tagato* configured compounds upfield shifts of 10–13 ppm for the vicinal carbon deshielded by the oxime hydroxyl, and 6–7 ppm only for the other, thus equally proving the *E*-geometry of the 1,5-anhydroketoximes. In the D-xylulose case though this upfield shift difference between ketose and ketoxime is nearly equalized—understandably, as the $^0S_2$ skew-boat conformation of the pyranoid ring levels the deshielding effects.

5. Experimental

5.1. General

Melting points were determined with a Bock hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20 °C using a cell of 1 dm path length; concentration (*c*) in g/100 mL and solvent are given in parentheses. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer in $CDCl_3$. Mass spectra were acquired on Varian MAT 311 spectrometer. Microanalyses were determined on a Perkin–Elmer 240 elemental analyzer. Analytical thin layer chromatography (TLC) was performed on precoated Merck plastic sheets (0.2 mm Silica Gel 60 F_{254}) with detection by UV light (254 nm) and either spraying with H_2SO_4 (50%) or by dipping into sulphuric acid/anisaldehyde reagent [containing anisaldehyde (1 mL), concd H_2SO_4 (9 mL) HOAc (10 mL) and MeOH (85 mL)] followed by heating at 110 °C for 10 min. Column and flash chromatography was carried out on Fluka Silica Gel 60 (70–230 mesh) using the specified eluents.

5.2. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-tagatose *E*-oxime 6

To a solution of hydroxylamine hydrochloride (7.4 g) in pyridine (50 mL) was added 10.0 g (30.3 mmol) of 2-acetoxy-D-galactal triacetate **5**[19,20] and the mixture was stirred at ambient temperature for 15 h, followed by pouring into water (350 mL). Extraction with $CHCl_3$ (5 × 100 mL) and consecutive washing of the combined extracts with 2 N H_2SO_4 (3 × 100 mL), water (100 mL), satd $NaHCO_3$ solution (100 mL) and water (50 mL), drying (Na_2SO_4) and evaporation to dryness in vacuo left a solid residue which was recrystallized from EtOH: 7.51 g (82%) of **6** as well-formed prisms of mp 154–156°C; $[\alpha]_D^{23} = -44.3$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.01, 2.03, 2.08 (three 3H-s, 3 AcCH_3), 3.94 (1H-d, 1-Ha), 3.98 (2H-m, 6-H_2), 4.18 (1H-dd, 5-H), 5.01 (1H-d, 1-He), 5.39 (1H-d, 4-H), 5.76 (1H-d, 3-H), 11.32 (1H-s, NO*H*), $J_{1,1}$ = 14.5, $J_{3,4}$ = 3.7, $J_{4,5}$ = 0 Hz. ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 20.2, 20.38, 20.42 (3 AcCH_3), 60.3 (C-1), 62.1 (C-6), 68.2 and 68.9 (C-3, C-4), 73.5 (C-5), 147.6 (C-2), 168.9, 169.9, 170.0 (3 Ac*C*O). Anal. Calcd for $C_{12}H_{17}NO_8$ (303.26): C, 47.52; H, 5.65; N, 4.62. Found: C, 47.58; H, 5.57; N, 4.53.

5.3. 1,5-Anhydro-D-tagatose *E*-oxime 7

Fifty millilitres of a 1 M NaOMe/MeOH solution were cooled to 0 °C with stirring and oxime **6** (3.03 g, 10 mmol) was added, TLC showing complete conversion within 20 min with the exclusive formation of **7** (R_f = 0.5 in *n*PrOH/water 7:3). The solution was diluted with 200 mL of MeOH and neutralised by stirring with Dowex 50 WX8, H^+ form for 10 min. The suspension was filtered and the resin was washed with methanol. Filtrate and washings were evaporated to a volume of about 50 mL whereupon crystallization occurred. The precipitate was redissolved by warming to allow smooth crystallization: 3.05 g (78%) of **7** as fine needles of mp 172–173 °C; $[\alpha]_D^{20} = -12.8$ (*c* 1, MeOH), $[\alpha]_D^{22} = -5.0$ (*c* 1, H_2O); lit.[6]: mp 176–179 °C; $[\alpha]_D = -9.2$ (*c* 0.5, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) after two reevaporations from D_2O to eliminate H, OH couplings: δ 3.47 (3H-m, 5-H, 6-H_2), 3.68 (1H-d, 1-Ha), 3.82 (dd, 1H, 4-H), 4.23 (dd, 1H, 3-H), 4.85 (1H, H-1e), 10.83 (1H-s, NOH), $J_{1,1}$ = 13.9, $J_{3,4}$ = 3.3, $J_{4,5}$ = 0.5 Hz. ^{13}C NMR (25.2 MHz, DMSO-d_6): δ 59.4 (C-1), 60.4 (C-6), 69.5 and 69.9 (C-3 and C-4), 78.3 (C-5), 153.7 (C-2). MS (FD): *m/e* = 177 (M^+). Anal. Calcd for $C_6H_{11}NO_5$ (177.16): C, 40.68; H, 6.26; N, 7.91. Found: C, 40.43; H, 6.19; N, 7.80.

5.4. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-tagatose 8

Stirring of **7** in acetonitrile solution (4.60 g, 15.2 mmol, in 50 mL) with acetaldehyde (3.0 mL) and 1 M HCl (15 mL) for 6 h at ambient temperature followed by dilution with water (250 mL), extraction with EtOAc (3 × 100 mL) and removal of the solvent from the organic layer gave a glassy syrup (4.5 g, 95%), which on the basis of ^{1}H NMR data in DMSO-d_6 comprised a 2:3 mixture of the keto form **8** and its monohydrate which due to its propensity for elimination of acetic acid to the enolone **11** in contact with silica gel was not attempted to separate. ^{1}H NMR (300 MHz, DMSO-d_6), *keto form*: δ 2.03, 2.06 (3H and 6H-s, 3 AcCH_3), 4.05 and 4.08 (two 1H-m, A and B part of an ABX system, 6-H_2), 4.09 and 4.38 (two 1H-d, 1-H_2), 4.54 (1H-m, X part of an ABX system, 5-H), 5.67 (dd, 1H, 4-H), 5.88 (1H-d, 3-H), $J_{1,1}$ = 14.5, $J_{3,4}$ = 4.0, $J_{4,5}$ = 0.9 Hz; *monohydrate*: 4.99 (1H-d, 3-H), 5.23 (dd, 1H, 4-H), 7.39 and 7.60 (two 1H-s, 2 OH, exchangeable with D_2O, $J_{3,4}$ = 5.3, $J_{4,5}$ = 5.8 Hz.

5.5. 1,5-Anhydro-D-tagatose 2

5.5.1. Deoximation of oxime 7

Acetaldehyde (1.7 mL, 30 mmol) and 1 M HCl (15 mL) were added to a suspension of **7** (1.43 g, 8 mmol) in acetonitrile (50 mL) and the mixture was stirred for 5 h at ambient temperature. The resulting clear solution was diluted with water (15 mL) and neutralised by stirring with an acidic resin (Amberlite IR 120 H^+ form) and the filtrate was evaporated to dryness in vacuo. The syrupy residue was then eluted from a silica gel column (3 × 45 cm) with *n*-propanol/water (7:3), to give upon evaporation of the product-carrying eluates in vacuo, finally at 0.01 mm, 1.08 g (83%) of **2** as an amorphous solid of R_f = 0.5 in 7:3 *n*-PrOH/water (extended spot); $[\alpha]_D^{21} = -7.9$ (*c* 0.9, H_2O); lit.[6]: $[\alpha]_D = -6.8$ (*c* 1.1, MeOH); MS (FD): *m/e* = 162 [M^+], 163 (M+1), 180 (M+H_2O). Anal.

Calcd for $C_6H_{10}O_5$ (162.14): C, 44.44; H, 6.22. Found: C, 44.29 H, 6.17.

NMR data in D_2O indicate an approximate 3:2 equilibrium between ketose and monohydrate form, as previously observed by Freimund and Köpper[7] for a product prepared by enzymatic oxidation of 1,5-anhydro-D-galactitol. ^{1}H NMR (500 MHz, D_2O), *keto form:* 3.58 (2H-m, 6-H_2), 3.92 (2H-m, H-1a, H-5), 4.04 (1H-d, H-1e) 4.20 (1H-dd, H-4), 4.45 (1H-d, H-3); $J_{1,1}$ = 14.8; $J_{3,4}$ = 3.9, $J_{4,5}$ = 0.9 Hz; *hydrate:* 3.23 (1H-d, H-1a), 3.43 (1H-m, H-5), 3.50 and 3.55 (AB part of an ABX system, 6-H_2), 3.54 (1H-d, H-3), 3.59 (1H-d, H-1e), 3.76 (1H-dd, H-4); $J_{1,1}$ = 12.0, $J_{3,4}$ = 3.8; $J_{4,5}$ = 1.0. ^{13}C NMR (75.2 MHz, D_2O). δ 210.1 (C-2, ketose), 92.5 (C-2, hydrate), 79.9/78.6 (C-5), 76.1/72.1 (C-3), 72.5/72.6 (C-1), 71.7/69.5 (C-4), 61.5/61.3 (C-6).

5.5.2. De-O-acetylation of 2-acetoxy-D-galactal triacetate 5

A solution of **5**[19,20] (2.0 g, 6 mmol) in dry MeOH (100 mL) was cooled to about −15 °C (salt–ice mixture) followed by the addition of 5 mL of 1 M NaOMe/MeOH solution and stirring of the mixture for 2 h at −15 °C, whereafter the solution was allowed to warm to 0 °C (∼1 h). Neutralization was then effected by stirring with Amberlite IR 120, H^+ form (10 min). Filtration and evaporation to dryness in vacuo gave a slightly yellowish, syrupy residue (910 mg) which was eluted from a Sephadex LH 20 column (2 × 30 cm) with water. Collecting the product-carrying eluates and removal of the solvent in vacuo, finally at 0.05 Torr, gave 820 mg (84%) of **2** as an amorphous solid, identical with the product described under 5.5.1.

5.5.3. Demercaptalization of dithioacetal 10

To a solution of 1.0 g (2.7 mmol) of **10** in 20 mL of water were added $CdCO_3$ (1.8 g, 10 mmol) and $HgCl_2$ (1.4 g, 5 mmol), and the mixture was stirred for 30 min at ambient temperature. The insoluble materials are subsequently removed by filtration through a layer of silica gel. The filtrate was then saturated with H_2S, and after another filtration with suction through silica gel the filtrate was neutralised with a weakly basic ion exchange resin (Lewatit MP 7080). Removal of the resin and concentration to dryness in vacuo left a viscous syrup which was purified by elution from a Sephadex LH 20 column (2 × 30 cm) with water. Removal of the solvent in vacuo from the product-carrying eluates and drying of the residue at 0.1 Torr gave 425 mg (69%) of a colourless foam, identical (TLC, NMR) with the product described under 5.5.1.

5.6. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-tagatose diethyldithioacetal 9

Ethanediol (3.7 mL, 50 mmol) and BF_3-etherate solution (10 mL) were added to a solution of 1.9 g (∼10 mmol) of anhydrotagatose triacetate **8** (mixture of ulose and hydrate as obtained under 5.4) in $CHCl_3$ (30 mL). After 15 min of stirring at ambient temperature, the solution was diluted with 50 mL of $CHCl_3$, neutralised by washing with 2 M NaOH and water (3 × 30 mL), dried (Na_2SO_4) and evaporated to dryness in vacuo. The resulting syrup, 2.23 g (61%) of **9**, was chromatographically uniform (R_f = 0.59 in toluene/acetone 2:1) and was used for the deacetylation (cf. below).

The analytical sample was purified by elution from silica gel with 40:1 CH_2Cl_2/EtOAc: syrup of $[\alpha]_D^{23} = +15.7$ (c 1, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 and 1.16 (two 3H-t, 2 EtS-CH_3), 2.00 and 2.05 (6H- and 3H-s, 3 AcCH_3), 2.65 (4H-m, 2 EtSCH_2), 3.74 and 3.99 (two 1H-d, 1-H_2), 3.99 (1H-m, 5-H), 4.17 (2H-m, 6-H_2), 5.25 (1H-dd, 4-H), 5.31 (1H-d, 3-H), $J_{1,1}$ = 12.5, $J_{3,4}$ = 3.7, $J_{4,5}$ = 3.2 Hz. ^{13}C NMR (25.2 MHz, $CDCl_3$): δ 60.3 (C-2), 61.2 (C-6), 66.6 (C-4), 70.3 (C-1), 73.9 and 74.6 (C-3 and C-5). Anal. Calcd for $C_{16}H_{26}O_7S_2$ (394.5): C, 48.71; H, 6.64. Found: C, 48.70; H, 6.72.

5.7. 1,5-Anhydro-D-tagatose diethyldithioacetal 10

A solution of 1.54 g (4.1 mmol) of triacetate **9** in 40 mL of 0.1 M methanolic sodium methoxide was stirred at 0 °C for 3 h and subsequently neutralised by stirring with Dowex WXl (H^+ form). Filtration and evaporation of the filtrate in vacuo afforded a syrup, which was chromatographed on silica gel (2 × 30 cm column) by elution with 2:1 toluene/EtOAc to result in 910 mg (87%) of **10** as a colourless syrup of $[\alpha]_D^{20} = -57$ (*c* 1.1, MeOH); R_f = 0.43 in *n*-butanone satd with water. ^{13}C NMR (25.2 MHz, D_2O): δ 61.9 (C-6), 62.4 (C-2), 67.4 (C-4), 72.9 (C-1), 74.6 and 81.5 (C-3 and C-5). MS (FD): *m/e* = 268 (M^+), 269 (M^+ + 1). Anal. Calcd for $C_{10}H_{20}O_4S_2$ (268.4): C, 44.75; H, 7.51. Found: C, 44.70; H, 7.62.

5.8. (6*S*)-4-Acetoxy-6-acetoxymethyl-2*H*-pyran-3(6*H*)-one 11

A 1.0 g portion of **8** and freshly molten NaOAc (2.0 g) were stirred in 50 mL of dry acetone for 1 h at room temperature. Filtration and evaporation of the filtrate in vacuo, and purification of the resulting syrup on silica gel column (2 × 30 cm) by fast elution with 3:1 *n*-hexane/EtOAc afforded 1.03 g (91%) of enolone **11** as a colourless syrup; $[\alpha]_D^{20} = -42.7$ (*c* 1.2, $CHCl_3$); lit.[7,21]: $[\alpha]_D^{20} = -17.7$ (*c* 0.34, CH_2Cl_2);[1] $[\alpha]_D = -43.7$ (*c* 1.7, $CHCl_3$).[17] ^{1}H and ^{13}C NMR data corresponded with those reported.[7,21]

5.9. 1,5-Anhydro-L-rhamnulose (1,5-anhydro-6-deoxy-L-fructose) 3

Five mmol (2.29 g) of **12**[8] was dissolved in 150 mL of anhydrous MeOH with slight warming, then cooled to −5 °C with vigorous stirring followed by the addition of 5 mL of 1 M NaOMe/MeOH solution. The mixture was allowed to warm to 0→+5 °C any precipitate occurring being dissolved within 10 min. After about 20 min (TLC monitoring with *n*-PrOH/water 9:1 or 7:3, R_f of product 0.65 and 0.72, respectively), the reaction was quenched by stirring with methanol-washed Amberlite IR 120 (H^+ form). Filtration and evaporation of the filtrate to dryness in vacuo left a syrup which was dissolved in water and eluted from a Sephadex LH 20 column (2 × 30 cm) with water. Evaporation of the product-carrying eluates in vacuo, finally at 0.1 Torr, gave 405 mg (69%) of **3** as an amorphous solid. ^{1}H NMR (500 MHz, D_2O): δ 1.20 (3H-d, CH_3), 3.16 (1H-t, H-4), 3.34 (1H-ddd, H-5), 3.37 (1H-d, H-1a), 3.44 (1H-d, H-3), 3.63 (1H-d, H-1e); $J_{1,1}$ = 12.3, $J_{3,4}$ = $J_{4,5}$ = 9.3, $J_{5,6}$ = 6.2 Hz. ^{13}C NMR (125.7 MHz, D_2O): δ 17.4 (C-6), 72.3 (C-1), 74.6 (C-4), 77.0 and 77.1 (C-3 and C-5), 93.2 (C-2): Anal. Calcd for $C_6H_{10}O_4$ (146.14): C, 49.31; H, 6.90. Found: C, 49.24; H, 6.96.

5.10. 3,4-Di-*O*-benzoyl-1,5-anhydro-L-rhamnulose *E*-oxime 14

2-Benzoyloxy-L-rhamnal dibenzoate **12**[8] (9.20 g, 20 mmol) was added to a solution of NH_3·HCl (3.5 g, 50 mmol) in 1:1 pyridine/EtOH (100 mL) and the mixture was kept at ambient temperature for one week and subsequently taken to dryness in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and successively washed with 2 M HCl (20 mL) and satd $NaHCO_3$ solution (2 × 20 mL), dried (Na_2SO_4), followed by removal of the solvent in vacuo and crystallization of the residue by trituration with EtOH: 6.35 g (86%) of **14** as colourless needles; mp 159–160 °C, $[\alpha]_D^{21} = +123$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (3H-d, CH_3), 3.75 (1H-m, 5-H), 4.00 and 5.12 (two 1H-d, 1-H_2), 5.36 (1H-t, 4-H), 5.94 (1H-d, 3-H), 7.4–8.0 (10H-m, 2 C_6H_5), 8.44 (1H-s, NOH); $J_{1,1}$ = 16.0, $J_{3,4}$ = $J_{4,5}$ = 8.0, $J_{5,6}$ = 5.9 Hz. Anal. Calcd for $C_{20}H_{19}NO_6$ (369.36): C, 65.03; H, 5.19; N, 3.79. Found: C, 64.91; H, 5.10; N, 3.71.

5.11. 3,4-Di-*O*-benzoyl-1,5-anhydro-L-rhamnulose 15

5.11.1. Deoximation of oxime 14

Stirring of **14** (3.69 g, 10 mmol) in acetonitrile solution (50 mL) with acetaldehyde (2.3 mL, 40 mmol) and 2 M HCl (5 mL, 10 mmol) was done overnight at ambient temperature followed by dilution with water (200 mL) and extraction with EtOAc (3 × 100 mL). Removal of the solvent from the extracts gave a syrup which crystallized from ether: 2.80 g (79%) of **15** as colourless needles of mp 123–124 °C, $[\alpha]_D^{21} = +109.9$ (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 (3H-d, CH_3), 4.11 (1H-m, 5-H), 4.16 and 4.33 (two 1H-d, 1-H_2), 5.56 (1H-t, 4-H), 5.86 (1H-d, 3-H), 7.4 and 8.0 (two m, 2 C_6H_5); $J_{1,1}$ = 15.8, $J_{3,4} = J_{4,5}$ = 7.9 Hz. Anal. Calcd for $C_{20}H_{18}O_6$ (354.34): C, 67.79; H, 4.90. Found: C, 67.69; H, 4.93.

5.11.2. Reductive debromination of ulosyl bromide 13

To a solution of **13**[8] (1.1 g, 2 mmol) in toluene (50 mL) were added azoisobutyronitrile (50 mg, 0.3 mmol) and tributyltin hydride (880 mg, 3 mmol) and the mixture was heated for 5 h at 90 °C, followed by cooling and washing with 10% aqueous KF solution (3 × 20 mL) and water. Drying ($MgSO_4$) and removal of the solvent in vacuo left an oily residue, uniform by TLC, which was freed from tin compounds by rapid chromatography on a silica gel column (2 × 20 cm) with 2:1 ether/*n*-pentane applying pressure to effect this operation within 10 min. The syrup remaining after evaporation of the eluate containing **15** crystallized on trituration with CH_2Cl_2/*n*-hexane to afford 505 mg (71%), identical with the product described under 5.11.1.

Longer contact of crude **15** with silica gel, for example, several hours on column purification, induced β-elimination of benzoic acid to the dihydropyran one **17**; it may be isolated in yields over 80% by slow elution of a silica gel column (3 × 30 cm) with 2:1 ether/*n*-pentane.

5.12. (6*S*)-4-Benzoyloxy-6-methyl-2*H*-pyran-3(6*H*)-one 16

Pyridine (0.3 mL) was added to a solution of **15** (1.42 g, 4 mmol) in $CHCl_3$ (10 mL) and the mixture was heated for 5 min, followed by evaporation to dryness in vacuo. Crystallization of the residue from MeOH afforded 810 g (87%) of **16** as colourless needles; mp 116 °C; $[\alpha]_D^{21} = -10.5$ (*c* 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.49 (3H-d, CH_3), 4.26 and 4.42 (two 1H-d, 2-H_2), 4.76 (1H-ddt, 6-H), 6.72 (1H-d, 5-H), 7.4-8.2 (5H-m, C_6H_5); $J_{2,6} = J_{5,6}$ = 1.9, $J_{6,CH_3} = 6.9$ Hz. Anal. Calcd for $C_{13}H_{12}O_4$ (232.23): C, 67.23; H, 5.21. Found: C, 67.26; H, 5.15.

5.13. (2*S*)-5,5-Dimethoxy-2-methyl-tetrahydropyran-4-one 17

Two millilitres of a 1 M NaOMe/MeOH solution were stirred into a suspension of enolone **16** (465 mg, 2 mmol) in dry MeOH (10 mL) and the mixture was neutralised after 5 min by addition of Amberlite IR (H^+ form). Filtration and evaporation of the filtrate to dryness gave a colourless oil, which can be purified by chromatography (2.5 × 25 cm silica gel column, elution with CCl_4/EtOAc 2:1) or distillation at 65 °C/0.3 Torr: 235 mg (68%) of **17**; $[\alpha]_D^{20} = - + 154.6$ (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (3H-d, CH_3), 2.43 and 2.71 (two 1H-d, 3-H_2), 3.29 and 3.39 (two 3H-s, 2 OCH_3), 3.76 (1H-ddq, 2-H), 3.38 and 4.24 (two 1H-d, 6-H_2); $J_{2,3}$ = 2.5 and 11.0, $J_{2,CH_3} = 6.1$, $J_{3,3}$ = 13.3, $J_{6,6}$ = 12.4 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.5 (CH_3), 41.4 (C-3), 49.9 (OCH_3), 71.0 (C-6), 75.6 (C-2), 98.3 (C-5), 202.7 C-4. MS (FD, 5 mA): *m*/*e* = 174 (M^+). Anal. Calcd for $C_8H_{14}O_4$ (174.18): C, 55.17; H, 8.10. Found: C, 54.98; H, 8.03.

5.14. 5-Benzoyloxy-2-methyl-4*H*-pyran-4-one (*O*-benzoyl-allomaltol) 22

N-Bromosuccinimide (360 mg, 2.5 mmol) and $BaCO_3$ (0.5 g) were added to a solution of enolone **16** (465 mg, 2 mmol) in EtOH-free CCl_4 (40 mL), and the mixture was irradiated with a 450 W IR lamp with vigorous stirring for 20 min, whereafter TLC in 19:1 CH_2Cl_2/EtOAc revealed the absence of educt in favour of several products. The major one, **22**, was isolated by filtration, evaporation of the filtrate to dryness and solution of the residue from a silica gel column (2 × 20 cm) with 19:1 CH_2Cl_2/EtOAc and crystallization from diisopropyl ether: 205 mg (44%) of **22** as needles of mp 128–129 °C. The product was identical (mixed mp, ^1H NMR) with an authentic sample.[22]

5.15. 3,4-Di-*O*-acetyl-1,5-anhydro-D-*threo*-pent-2-ulose *E*-oxime 25

A mixture of 2,3,4-tri-*O*-acetyl-1,5-anhydro-D–D-*threo*-pent-1-enitol **23**[20] (1.03 g, 4 mmol), hydroxylamine hydrochloride (1.0 g), tetrahydrofuran (10 mL) and acetate buffer (pH 4.5) was stirred for 20 h at ambient temperature, followed by gradual neutralization with satd $NaHCO_3$ solution and extractions with $CHCl_3$ (3 × 20 mL). The $CHCl_3$ extracts were washed with water, dried (Na_2SO_4) and taken to dryness in vacuo. The syrupy residue crystallized on trituration with EtOH: 730 mg (79%) of **25** as needles of mp 103–104 °C; $[\alpha]_D^{22} = -58.3$ (*c* 0.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.06 and 2.08 (two 3H-s, 2 Ac CH_3), 3.92 (1H-dd, 5-Hax), 4.28 and 4.52 (two 14.1 Hz-d, 1H each, 1-H_2), 4.66 (1H-dd, 5-Heq), 4.90 (1H-sx, 4-H), 5.36 (1H-d, 3-H), 11.48 (1H-s, NO*H*), $J_{1,1}$ = 14.1, $J_{3,4}$ = 5.0, $J_{4,5}$ = 3.1 and 5.0, $J_{5,5}$ = 12.2 Hz. Anal. Calcd for $C_9H_{13}NO_6$ (231.20): C, 46.75; H, 5.67; N, 6.06. Found: C, 46.70; H, 5.59; N, 6.09.

5.16. 3,4-Di-*O*-benzoyl-1,5-anhydro-D-*threo*-pent-2-ulose *E*-oxime 26

Hydroxylamine hydrochloride (10.0 g, 1.4 mmol) was added to a solution of 2,3,4-tri-*O*-benzoyl-1,5-anhydro-D-*threo*-pent-1-enitol **24**[20] (10.0 g, 22.5 mmol) in pyridine (60 mL) and the mixture was stirred for 1 h and then stood for 5 d at ambient temperature, followed by stirring into water (1.5 mL). The precipitate formed was filtered off, washed with water, dried (Na_2SO_4) and recrystallized from $CHCl_3$/EtOH to give 9.4 g (75%) of colourless needles of mp 194–196 °C, which consisted of a 10:1 mixture (^1H NMR) of the *E*-oxime **26** (R_f = 0.56 in 10:1 CH_2Cl_2/EtOAc) and the respective *Z*-isomer (R_f = 0.49).

A 500 mg sample was subjected to elution from a silica gel column (2 × 20 cm) with CH_2Cl_2/EtOAc 30:1, the first fractions containing 220 mg of the pure *E*-isomer; mp 198–199 °C; $[\alpha]_D^{23} = -111$ (*c* 0.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 3.89 and 4.13 (two 1H-dd, 5-H_2), 4.48 and 4.67 (two 1H-d, 1-H_2), 5.37 (1H-ddd, 4-H), 5.86 (1H-d, 3-H), $J_{1,1}$ = 15.1, $J_{3,4}$ = 5.6, $J_{4,5}$ = 3.4 and 4.5, $J_{5,5}$ = 12.7 Hz. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 61.7 (C-1), 67.4 (C-5), 69.8 (C-3), 71.0 (C-4), 151,4 ((C-2). Anal. Calcd for $C_{19}H_{17}NO_6$ (355.33): C, 64.22; H, 4.82; N, 3.94. Found: C, 64.08; H, 4.75; N, 3.84.

The further fractions consisted of *E*/*Z*-mixtures in various ratios, which were not further separated. ^1H NMR (500 MHz, $CDCl_3$ for *Z*-form): δ 4.10 (2H-m, 5-H_2), 4.28 and 4.37 (two 13.0 Hz-d, 1H each, 1-H_2), 5.27 (1H-ddd, 4-H), 6.50 (d, 1H, 3-H), $J_{1,1}$ = 13.0, $J_{3,4} = J_{4,5}$ = 1.3-1.4 Hz; most distinct difference between the *E*/*Z*-isomers is the chemical shift for H-3: 5.86 (*E*) vs. 6.50 ppm for the *Z*-form.

5.17. 1,5-Anhydro-D-*threo*-pent-2-ulose *E*-oxime 27

Oxime **26** (3.55 g, 10 mmol, in the form of its 10:1 *E*/*Z*-mixture obtained above) was dissolved in 50 mL cooled (0 °C) 1 M NaOMe/

MeOH solution and stirred for 1 h. Subsequent neutralization with Dowex 50 WX8 (H^+ form) filtration and evaporation to dryness in vacuo left a syrup which was dissolved in water (30 mL) and washed with ether to remove methyl benzoate. The syrup remaining after evaporation of the aqueous phase to dryness in vacuo crystallized from water/*i*-propanol. Recrystallization from the same solvents afforded 0.93 g (63%) of **27** as fine prisms of mp 129.5–130.5 °C; $[\alpha]_D^{20} = +14.8$ (*c* 1, H_2O). ^{1}NMR (300 MHz, DMSO-d_6): δ 3.45 and 3.76 (two 1H-dd, AB part of ABX system, 5-H_2), 3.54 (1H-m, X part, 4-H), 3.90 (1H-dd, 3-H), 4.04 and 4.48 (two 1H-d, 1-H_2), 5.01 and 5.32 (two 1H-d, 2 OH), 10.83 (1H-s, NOH); $J_{1,1}$ = 13.8, $J_{3,4}$ = 4.2, $J_{4,5}$ = 2.2 and 3.6, $J_{5,5}$ = 11.6 Hz. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 58.8 (C-1), 67.3 (C-5), 69.8 (C-3), 70.1 (C-4), 153.5 (C-2). Anal. Calcd for $C_5H_9NO_4$ (147.13): C, 40.81; H, 6.17; N, 9.52. Found: C, 40.72; H, 6.12; N, 9.40.

5.18. 3,4-Di-*O*-benzoyl-1,5-anhydro-D-pentulose 28

5.18.1. Monohydrate

Pentulose oxime **26** (10.0 g, 30 mmol), in the form of its 10:1 *E*/*Z*-mixture as obtained above, was stirred with a mixture of acetonitrile (250 mL), 2 M HCl (18 mL) and acetaldehyde (10 mL) at ambient temperature for 18 h and subsequently poured into water (1 L) with vigorous stirring. The resulting precipitate was filtered, washed with water and dried ($CaCl_2$). Dissolution in the minimum amount of methanol and trituration with 2:1 cyclohexane/ether resulted in crystallization: 9.3 g (92%) of **28**-monohydrate; mp 89–90 °C, $[\alpha]_D^{20} = -131$ (*c* 0.6, $CHCl_3$). ^{1}NMR (300 MHz, DMSO-d_6): δ 3.47 and 3.66 (two 11.5 Hz-d, 1H each, 1-H_2), 3.54 and 4.06 (two 1H-ddd, 5-H_2), 5.23 (1H-ddd, 4-H), 5.38 (d, 1H, 3-H), 6.20 and 6.28 (two 1H-s, 2 OH, exchangeable with D_2O), 7.4-8.1 (10H-m, 2 C_6H_5); $J_{1,1}$ = 11.5, $J_{3,4}$ = 9.3, $J_{4,5}$ = 5.0 and 9.7, $J_{5,5}$ = 11.0 Hz. ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 66.7 (C-1), 70.1 (C-4), 78.5 (C-5), 75.9 (C-3), 91.7 (C-2). Anal. Calcd for $C_{19}H_{16}O_6 \cdot H_2O$ (358.33): C, 63.68; H, 5.06. Found: C, 63.54; H, 4.95.

5.18.2. Keto-form

The reaction mixture resulting from a deoximation as described above (after stirring for 18 h), was subjected to a different workup, by elution with water (500 mL), extraction with EtOAc (3 × 200 mL), washing of the combined extracts with water, drying (Na_2SO_4) and removal of the solvent in vacuo. The resulting syrup crystallized CH_2Cl_2/*n*-hexane or CCl_4: 8.1 g (75%) of **28** as an amorphous product of mp 93–95 °C and $[\alpha]_D^{20} = -117$ (*c* 0.6, $CHCl_3$), which appeared (NMR) to contain only small amounts of the monohydrate. ^{1}H NMR (300 MHz, acetone-D_6): δ 4.16 (1H-dd, 5-Ha), 4.21 and 4.44 (two 1H-d, 1-H_2), 4.46 (1H-ddd, 5-He), 5.73 (1H-ddd, 4-H), 6.13 (1H-d, 3-H); $J_{1,1}$ = 15.0, $J_{1,5}$ = 1.1, $J_{3,4}$ = 9.0, $J_{4,5}$ = 8.0 and 5.1, $J_{5,5}$ = 12 Hz. ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 67.5 (C-1), 71.6 (C-4), 73.4 (C-5), 77.3 (C-3), 199.4 (C-2). Anal. Calcd for $C_{19}H_{16}O_6$ (340.32): C, 67.05; H, 4.75. Found: C, 66.85; H, 4.80.

5.19. 1,5-Anhydro-D-xylulose (1,5-anhydro-D-*threo*-pentulose) 4

5.19.1. Deoximation of oxime 27

Acetaldehyde (0.56 mL, 10 mmol) and 1 M HCl (5 mL) were added to a suspension of oxime **27** (440 mg, 3 mmol) in acetonitrile (15 mL) and the mixture was stirred for 5 h at ambient temperature. The resulting clear solution was diluted with water (5 mL) and neutralised by stirring with an acidic resin (Amberlite IR 120 H^+ form) and the filtrate was evaporated to dryness in vacuo. The syrupy residue was then eluted from a silica gel column (2 × 15 cm) with 7:3 *n*-propanol/water, to give upon evaporation of the product-carrying eluates in vacuo, finally at 0.01 mm, 265 mg (67%) of **4** as a fluffy solid. ^{1}H NMR (300 MHz, D_2O, 2 h after solution): δ 3.38 and 3.69 (two 1H-d, 1-H_2), 3.40 (1H-t, 4-H), 3.54 (1H-d, 3-H), 3.60 and 3.94 (two 1H-dd, 5-H_2), $J_{1,1}$ = 12.4, $J_{3,4}$ = 8.7, $J_{4,5}$ = 7.9 and 4.7 Hz. ^{13}C NMR (75.5 MHz, D_2O): δ 66.9 (C-1), 70.2 (C-4), 71.9 (C-3), 78.2 (C-5), 92.5 (C-2). Anal. Calcd for $C_5H_8O_4$ (132.11): C, 45.45; H, 6.10. Found: C, 45.34; H, 6.00.

5.19.2. De-O-acetylation of 2-acetoxy-D-xylal diacetate 23

A methanolic solution of **23**[16] (1.29 g, 5 mmol, in 80 mL) was cooled to −15 °C (ice–salt mixture), and upon dropwise addition of 1 M NaOMe/MeOH (5 mL) the mixture was allowed to come to 0 °C within about 1 h (TLC monitoring with *n*-PrOH/water 7:3). Subsequent quenching by stirring methanol-washed Amberlite IR 120 (H^+ form) into the still cold solution. Filtration, evaporation of the filtrate in vacuo, elution of the residue from an LH 20 Sephadex column (2 × 25 cm) with water, evaporation of the product-carrying eluates and drying, finally at 0.1 Torr, gave 440 mg (67%) of **4** as a foam, identical with respect to ^{1}H and ^{13}C NMR data with the product described above.

Desulfurization of dithioacetal by stirring an aqueous solution with $CdCO_3/HgCl_2$ as described for **10**→**2** and analogous workup similarly gave **4** in 75% yield.

5.20. 3,4-Di-*O*-benzoyl-1,5-anhydro-D-*threo*-pentulose diethyldithioacetal 29

Ethanthiol (7.0 mL) and BF_3 etherate (5 mL) were added to a suspension of ulose monohydrate **28**·H_2O (3.2 g, 8.9 mmol) in $CHCl_3$ (30 mL). The mixture was stirred for 5 min followed by dilution with $CHCl_3$ (100 mL) and consecutive washings with 2 M NaOH and water (3 × 30 mL). Drying (Na_2SO_4) and evaporation in vacuo left a syrup which was purified by elution from silica gel (3 × 30 cm column) with 20:1 cyclohexane/EtOAc. Removal of the solvents from the product-carrying fractions (R_f = 0.57 in 2:1 cyclohexane/EtOAc) afforded 3.5 g (88%) of **29** as a colourless syrup; $[\alpha]_D^{20} = -121.4$ (*c* 0.8, $CHCl_3$). ^{1}NMR (300 MHz, DMSO-d_6): δ 1.10 and 1.24 (two 3H-t, SEt-CH_3), 2.70 (4H-m, SEt-CH_2), 3.72 and 4.21 (two 1H-dd, 5-H_2), 3.90 and 4.07 (two 1H-d, 1-H_2), 5.69 (1H-ddd, 4-H), 5.80 (1H-d, 3-H); $J_{1,1}$ = 12.6, $J_{3,4}$ = 9.5, $J_{4,5}$ = 5.5 and 9.5 Hz, $J_{5,5}$ = 10.5 Hz. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 14.1 and 14.2 (2 SEt-CH_3), 22.4 and 22.5 (2 SEt-CH_2), 62.1 (C-2), 67.2 (C-5), 69.1 (C-4), 72.1 (C-1), 76.0 (C-3). Anal. Calcd for $C_{23}H_{26}O_5S_2$ (446.6): C, 61.86; H, 5.87. Found: C, 61.76; H, 5.91.

5.21. 1,5-Anhydro-D-*threo*-pentulose diethyldithioacetal 30

To a cooled (0 °C) 0.1 M NaOMe/MeOH solution (100 mL) was added 5.5 g (12.3 mmol) of dibenzoate **29** and the mixture was stirred for 3 h at this temperature followed by neutralization with an acidic resin (Dowex 50, H^+ form). Filtration and evaporation in vacuo left a syrup which was dissolved in water (50 mL). Washing with ether (2 × 5 mL), evaporation to dryness and purification of the syrupy residue by elution from silica gel (2.5 × 30 cm) with 20:1 CH_2Cl_2/EtOAc gave 2.8 g (95%) of a uniform (TLC) amorphous product, which upon freeze drying of an aqueous solution crystallized; mp 51–52 °C; $[\alpha]_D^{20} = -79.3$ (*c* 1.1, MeOH). ^{1}NMR (300 MHz, DMSO-d_6): δ 1.13 and 1.14 (two 3H-t, SEt, CH_3), 2.72 (4H-m, SEt-CH_2), 3.02 (1H-m, 4-H), 3.41 (1H-dd, 3-H), 3.46 and 3.76 (two 1H-d, 1-H_2), 3.80 (2H-m, 4-H, 5-H), 5.01 and 5.40 (two 1H-d, 2 OH); $J_{1,1}$ = 12.2, $J_{3,4}$ = 8.1. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 14.2 and 14.4 (2 SEt-CH_3), 21.8 and 22.6 (2 SEtCH_2), 64.1 (C-2), 67.7 (C-4), 71.1 (C-5), 73.3 (C-1), 79.8 (C-3). Anal. Calcd for $C_9H_{18}O_3S_2$ (238.4): C, 45.35; H, 7.61. Found: 45.18; H, 7.65.

5.22. 4-Benzoyloxy-2*H*-pyran-3(6*H*)-one 31

A few drops of pyridine were added to a solution of 680 mg (2 mmol) of ulose dibenzoate **29** in $CHCl_3$ (10 mL) and the mixture was heated at reflux for 10 min. Evaporation to dryness and recrys-

tallization of the residue from methanol gave 560 mg (82%) of **31** as colourless needles; mp 111–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.32 (2H-s, 2-H_2, 4.61 (2H-d, 6-H_2), 4.61 (1H-t, 5-H); $J_{5,6}$ = 4.0 Hz. MS (FD): *m/e* = 218 (M^+). Anal. Calcd for $C_{12}H_{10}O_4$ (218.2): C, 66.05; H, 4.62. Found: C, 66.01; H, 4.54.

5.23. 3,4-6-Tri-*O*-acetyl-1,5-anhydro-D-sorbose *E*-oxime 35

A solution of hydroxylamine hydrochloride (2.50 g) and of syrupy 2-acetoxy-D-gulal triacetate **32**[11] (3.90 g, 11.8 mmol) in 30 mL of 1:1 pyridine/EtOH was made to stand for 6 h at ambient temperature and then stirred into water (300 mL) followed by extraction with $CHCl_3$ (3 × 50 mL) and consecutive washings of the combined extracts with 2 N HCl (3 × 50 mL), water (50 mL) satd $NaHCl_3$ solution (50 mL) and water (50 mL). Drying (Na_2SO_4) and evaporation to dryness in vacuo left 3.40 g (95%) of a solid residue which by ^{1}H NMR proved to be a 4:1 mixture of *E* and *Z* isomers.

Chromatography on a silica gel column (3 × 40 cm, elution with 10:1 CH_2Cl_2/EtOAc) and processing of the first product-carrying fraction gave a syrup upon evaporation in vacuo which gradually crystallized on drying at 0.01 Torr overnight: 2.85 g (80%) of *E*-oxime **35**; mp 118–120 °C; $[\alpha]_D^{20} = -15.1$ (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.03, 2.09 and 2.10 (three 3H-s, 3 Ac-CH_3), 3.96 (1H-m, 5-H), 4.11 (2H-m, 6-H_2), 4.01 and 4.95 (two 13.1 Hz-d, 1H each, 1-H_2), 5.00 (1H-dd, 4-H), 5.23 (1H-d, 3-H), 11.63 (1H-s, NO*H*): $J_{1,1}$ = 13.1, $J_{3,4}$ = 3.2 Hz. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 59.1 (C-1), 62.6 (C-6), 67.9 and 68.6 (C-3 and C-4), 71.8 (C-5), 148.0 (C-2). MS (FD): *m/e* = 304 (M+1), 303 (M^+). Anal. Calcd for $C_{12}H_{17}NO_8$ (303.26): C, 47.52; H, 5.65; N, 4.62. Found: C, 47.60; H, 5.60; N, 4.45.

The fractions eluted next contained the *E*/*Z* isomers in varying compositions as evidenced by ^{1}H NMR, the *Z*-oxime being clearly differentiated by shifts of H-3 from 5.23 (*E*-form) to 6.03 and one of the H-1 protons from 4.95→4.37 ppm.

5.24. 3,4-6-Tri-*O*-acetyl-1,5-anhydro-D-psicose *E*-oxime 36

A mixture of hydroxylamine hydrochloride (2.1 g, 20 mmol), pyridine (10 mL), EtOH (10 mL) and 3.30 g (10 mmol) of 2-acetoxy-D-allal triacetate **33**[11,12] was stirred for 6 h at ambient temperature and subsequently poured into water (300 mL). Extraction with $CHCl_3$ (3 × 50 mL), and consecutive washings of the combined extracts with 2 M HCl, water, satd $NaHCO_3$ solution and again water, drying (Na_2SO4) and removal of the solvent in vacuo left 3.0 g of a crystalline product, which was recrystallized from EtOH: 2.48 g (82%) of **36**; mp 129–131 °C; $[\alpha]_D^{20} = +27.2$ (*c* 0.84, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.98, 2.01 and 2.10 (three H-s, 3 Ac-CH_3), 4.00 (1H-m, H-5), 4.02 (1H-d, H-1a), 4.17 (2H-m, 6-H_2), 4.84 (1H-dd, 4-H), 4.91 (1H-d, H-1e), 5.71 (1H-d, H-3), 11.62 (1H-s, NO*H*); $J_{1,1}$ = 14.5, $J_{3,4}$ = 3.5, $J_{4,5}$ = 8.9 Hz. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ 20.3, 20.4, 20.5 (3 Ac-CH_3), 59.6 (C-1), 62.7 (C-6), 68.1 and 68.6 (C-3, C-4), 72.7 (C-5), 149.2 (C-2). MS (FD): *m/e* = 304 (M+1), 303 (M^+). Anal. Calcd for $C_{12}H_{17}NO_8$ (303.26): C, 47.52; H, 5.65; N, 4.62. Found: C, 47.30; H, 5.55; N, 4.53.

5.25. 3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,5-anhydro-D-fructose *E*-oxime 37

To a solution of $NH_2OH{\cdot}HCl$ (620 mg, 1 mmol) in pyridine (10 mL) was added 620 mg (1 mmol) of 2-acetoxy-cellobial hexaacetate **34**[13] and the mixture was stirred at ambient temperature for 7 h, subsequently diluted with water (10 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were washed with water, dried (Na_2SO_4) and taken to dryness in vacuo. The syrupy residue crystallized on trituration with ethanol: 430 mg (87%) of **37**; mp 125–127 °C; $[\alpha]_D^{21} = -22.3$ (*c* 0.3, $CHCl_3$); R_f = 0.31 (benzene/EtOAc 10:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.99, 2.01 and 2.03 (3s, 18H, 6 Ac-CH_3), 4.03 (15.1 Hz-d, 1H, 1-Ha), 4.03–4.30 (5H-m, 5-H, 6-H_2, 6′-H_2), 4.91 (15.1 Hz-d, 1-He), 5.0-5.7 (5H-m, 4-H, 1′-H through 4′-H), 6.80 (1H-d, 3-H), 11.4 (14-s, NO*H*). Anal. Calcd for $C_{24}H_{33}NO_{16}$ (494.51): C, 58.29; H, 6.52; N, 2.83. Found: C, 58.17; H, 6.48; N, 2.74.

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