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 deoximation 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,3,4 a food additive5 or a pharmaceutical6 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 1H and 13C 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 H2O already previously observed by Freimund and Köpper7—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.

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
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-α-D-tagatose 2 by Zemplén methanolation to 10 and subsequent desulfurization. By far the most simple generation of 1,5-anhydro-α-D-tagatose, however, proved to be the direct Zemplén methanolation 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 ketone 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, the 2-benzoyloxy-L-rhamnal dibenzoate 12 was similarly subjected to Zemplén methanolation 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 to 0 °C) in high dilution and short-reaction times (3–5 min), the parent sugar, 1,5-anhydro-L-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·H₂O.

The well-crystallizing dibenzoate of 1,5-anhydro-α-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 methanolation 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 acyl 18→17). Such a course receives some credence by the detection of 19 by 1H NMR and TLC on brief methanolation, and by the obtention of benzoyl-allomaltol 22 on the attempt to anomerically refunctonalize dihydropyranone 16 by photobromination with NBS (Scheme 3). As observed for the 6-benzoyloxyethyl analogue of 16, 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 (arrows in 20 and 21, respectively).

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**Scheme 1.** Reactions and conditions: (a) NH₂OH·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 (BF₃, 15 min, rt, 61%; (g) NaOAc/acetonitrile, 1 h, rt, 91%; (h) CdCO₃/HgCl₂ in water, 30 min, rt, 69%; (i) NaOMe/MeOH, 3 h, 0 °C, 87%.

**Scheme 2.** Reactions and conditions: (a) NaOMe/MeOH, −10 to 0 °C, 84%; (b) NBS/MeOH in CH₂Cl₂, 30 min, rt, 75%; (c) NH₂OH/pyridine in EtOH, 5 d, rt, 86%; (d) Bu₃SnH/AIBN in toluene, 5 h, 90 °C, 71%; (e) acetaldehyde/HCl in MeCN, 15 h, rt, 82%; (f) pyridine in CHCl₃, 5 min reflux, 87%; (g) NaOMe/MeOH, 5 min, rt, 68%. 

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2.3. 1,5-Anhydro-α-xylulose

Application of the methodology developed for hydroxylaminolysis and Zemplén deacylation to the 2-hydroxy-α-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 diethylidithio 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 1H and 13C 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-α-xylulose 4 could be effected from the oxime 27 by transoximation, from the diethylidithio acetal 30 by desulfurization and, preparatively most straightforward, by Zemplén methanolysis of the 2-acetoxy-α-xylal diacetate 23. The resulting 1,5-anhydro-α-pentulose was characterized by NMR to be the monohydrate in aqueous solution, whilst in DMSO-d6 or in pyridine-d5, spectra turned out to be unusually complex indicating the presence of dimeric forms.

With respect to the conformations adopted by 1,5-anhydro-α-xylulose 4 and its derivatives 25–30, 1H NMR data—most notably their J1,4 and J4,5 values—reveal the uloses 4 and 28, respectively, and their monohydrates to be in the C3 conformation, whilst the couplings of the oximes 25–27 based on J5,4 and J4,5 values of 2.5–4 Hz are best interpreted by their adoption of the S2 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-xylulose 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 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-gulal, 2-hydroxy-D-allal, 2-hydroxy-D-cellobial and lactal analogues, should there be need for their enol ester hydroxylaminolysis smoothly provides the respective E-oximes 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-α-sorbose from 32 and its α-psico analogue from 33. In similar fashion, the readily accessible disaccharide-derived 2-hydroxyglycal esters and their benzoylated maltal, cellobial and lactal analogues 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-α'-glycosidoloses 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-geometry with the oxime hydroxyl pointing towards the anomeric carbon rather than C-3, hence establishing the E-configuration for oximes 40–45.

In the o-tagato and o-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 o-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 13C 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 13C chemical shifts of the carbons vicinal to the carboxyl, respectively, oximinocarbonyl group. As documented by vast literature data,17,18 the 13C 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. 13C 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).

In the o-xylulo case 37 and 39–40 to their 2-ulos conclusive 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.

Table 1

<table>
<thead>
<tr>
<th>Configuration</th>
<th>1H NMR data for H-1 and the anomeric hydrogens of 1,5-anhydroketoses and acylated derivatives in comparison to those of their E-oximes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,5-Anhydroketoses</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>X = O</td>
</tr>
<tr>
<td></td>
<td>H-1e</td>
</tr>
<tr>
<td>o-Tagato</td>
<td>4.04</td>
</tr>
<tr>
<td></td>
<td>3.88</td>
</tr>
<tr>
<td>o-Rhamnulo</td>
<td>4.33</td>
</tr>
<tr>
<td>o-Xylulo</td>
<td>4.44</td>
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</tbody>
</table>

- 1H Anhydro-α-fructose I and its o-xylulo analogue 4 adopt in water (D2O) the 2,2-dihydroxyhydrate (hydrate) form, and hence are not suited for comparison.
- Data from this paper.
- Signal not resolved from glycosyl protons.
Analogous shift differences are observed for the $^{13}$C resonances of the four ketose/oxime examples listed in Table 2: in the o-fructo and o-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 $\alpha$-xylulose case though this upfield shift difference between ketose and ketoxime is nearly equalized—understandably, as the $\delta S_2$ 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 5078. Microanalyses were determined 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.

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

To a solution of hydroxylamine hydrochloride (7.4 g) in pyridine (50 mL) was added 10.0 g (30.3 mmol) of 2-acetoxy-o-galactal triacetate $^9$ 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 eluates in vacuo, finally at 0.01 mm, 1.08 g of a 1,5-anhydro-o-fructose $^1$ was obtained.

Table 2

<table>
<thead>
<tr>
<th>Configuration</th>
<th>1,5-Anhydroketoses</th>
<th>1,5-Anhydroketoximes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Compd.</td>
<td>C-1</td>
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<tr>
<td>o-Fructo</td>
<td>1$^*$</td>
<td>-</td>
</tr>
<tr>
<td>o-Fructo</td>
<td>28</td>
<td>72.5</td>
</tr>
<tr>
<td>o-Fructo</td>
<td>39</td>
<td>72.5</td>
</tr>
<tr>
<td>o-Tagato</td>
<td>2</td>
<td>72.5</td>
</tr>
<tr>
<td>o-xylulose</td>
<td>28</td>
<td>67.5</td>
</tr>
</tbody>
</table>

$^*$ 1,5-Anhydro-o-fructose 1 forms dimers in the solid state and the hydrate in water, hence is unsuited for comparison.

5.4. 3,4,6-Tri-O-acetyl-1,5-anhydro-o-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. $^3$H NMR (300 MHz, DMSO-d$_6$), keto form: $\delta$ 2.03, 2.06 (3H and 6H-s, 3 AcC$_2$), 4.95 and 4.98 (two 1H-d, 1-Ha, 1-Hb); 3.54 and 3.59 (two 1H-d, 1-Hc, 1-Hd) ppm. 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 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); $[\alpha]_D^{20} = -5.0$ (c 1, H$_2$O); lit.$^6$: mp 176–179 °C; $[\alpha]_D = -9.2$ (c 0.5, MeOH). $^3$H NMR (300 MHz, DMSO-d$_6$) after two reevaporations from D$_2$O to eliminate H, OH couplings: $\delta$ 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, 1-He), 10.83 (1H-s, NOH), J$_{1,14} = 13.9$, J$_{14,15} = 3.3$, J$_{1,5} = 0.5$ Hz. $^{13}$C NMR (25.2 MHz, DMSO-d$_6$); $\delta$ 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$_{16}$H$_{21}$NO$_7$: C, 59.0; H, 6.9; N, 7.0.

5.5. 1,5-Anhydro-o-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 (extended spot); $[\alpha]_D^{20} = -7.9$ (c 0.9, H$_2$O); lit.$^6$: $[\alpha]_D = -6.8$ (c 1.1, MeOH); MS (FD): m/e = [162 (M$^+$), 163 (M+1), 180 (M+H$_2$O)]. Anal.
5.5.2. De-O-acetylation of 2-acetoxy-α-galacto-triactetate 5

A solution of 5 \( (2.0 \text{ g}, 6 \text{ mmol}) \) in dry MeOH (100 mL) was cooled to about \(-15 ^\circ \text{C} \) (salt–ice mixture) followed by the addition of 3 mL of 1 M NaOMe/MeOH solution and stirring of the mixture for 2 h at \(-15 ^\circ \text{C} \), whereafter the solution was allowed to warm to 0 \(^\circ\)C (\(-1 \) h). Neutralization was then effected by stirring with Amberlite IR 120, H\(^+\) form (10 min). Filtration and evaporation to dryness in vacuo left a syrup which was dissolved in water and eluted from a Sephadex LH 20 column (\(2 \times 30 \text{ cm} \)) 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 was added 

\[
\text{CHCl}_3 (1.8 \text{ g}, 10 \text{ mmol}) \quad \text{and HgCl}_2 (1.4 \text{ g}, 5 \text{ mmol}),
\]

and the mixture was stirred for 30 min at ambient temperature. The insoluble materials were subsequently removed by filtration through a layer of silica gel. The filtrate was then saturated with H$_2$S, and after another filtration with suction through silica gel the filtrate was neutralized 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 (\(2 \times 30 \text{ cm} \)) 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-α-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 (50 mmol) of 1,5-anhydro-D-galactitol. 1H NMR (500 MHz, CDCl$_3$): 3.58 (2H-m, 6-H$_2$), 3.92 (2H-m, 3-H$_2$), 3.75 (3H-d, 1-H$_2$), 3.95 (1H-t, H-4), 3.99 (1H-m, 5-H$_2$), 4.04 (1H-d, H-3)$_{\text{a}}$, 4.20 (1H-dd, H-4)$_{\text{a}}$, 4.45 (1H-d, H-3)$_{\text{b}}$, 5.25 (1H-dd, 4-H), 5.31 (1H-d, 3-H)$_{\text{b}}$, 6.14 (1H-d, C-5)$_{\text{b}}$, 6.15 (1H-d, C-4)$_{\text{b}}$, 6.25 (1H-d, C-3)$_{\text{b}}$. Anal. Calcd for C$_{20}$H$_{19}$NO$_6$ (369.36): C, 65.03; H, 5.19; N, 3.79. Found: C, 64.97; H, 5.09; N, 3.79.

5.7. 1,5-Anhydro-α-tagatose diethylidithioacetal 10

A solution of 1.54 g (4.1 mmol) of triactetate 9 in 40 mL of 0.1 M methanolic sodium methoxide was stirred at 0 \(^\circ\)C for 3 h and subsequently neutralised by stirring with Dowex WXI (H\(^+\) form). Filtration and evaporation of the filtrate in vacuo afforded a syrup, which was chromatographed on silica gel (2 \(\times 30 \text{ cm} \)) by elution with 2:1 toluene/EtOAc to result in 910 mg (87\%) of 10 as a colourless syrup of \(m/e = 57 \) (c 1, MeOH); R$_f$ = 0.43 in n-butanol/methanol 910 mg (87\%) of 10 as a colourless syrup of \(m/e = 57 \) (c 1, MeOH); R$_f$ = 0.43 in n-butanol/MeOH solution. The mixture was allowed to warm to 0\(-+5 ^\circ\)C any precipitate occurring being dissolved within 10 min. After about 20 min (TLC monitoring with n-ProOH/water 9:1 or 7:3, R$_f$ = 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 (\(2 \times 30 \text{ cm} \)) 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, identical with the product described under 5.5.1.
5.11. 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

5.12. Reductive deamination of ulosyl bromide 13

As colourless needles of mp 123–124 °C from a silica gel column (200 mL). Removal of the solvent from the extracts gave a syrup which crystallized from ether: 2.80 g (79%) of

5.13. (2S)-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 heated for 5 min, followed by evaporation of dryness to vacuo. Crystallization of the residue from MeOH afforded 810 g (87%) of

5.14. 5-Benzoyloxy-2-methyl-4H-pyran-4-one (O-benzoylallomaltol) 22

N-Bromosuccinimide (360 mg, 2.5 mmol) and BaCO₃ (0.5 g) were added to a solution of enolone 16 (465 mg, 2 mmol) in EtOH-free CCl₄ (40 mL), and the mixture was irradiated with a 450 W IR lamp with vigorous stirring for 20 min, whereafter TLC in 19:1 CH₂Cl₂/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 CH₂Cl₂/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-o-three-pent-2-ulose E-oxime 25

A mixture of 2,3,4-tri-O-acetyl-1,5-anhydro-o-three-pent-1-enitol 23 (1.03 g, 4 mmol), hydroxylamine hydrochloride (1.0 g), and acetate buffer (pH 4.5) was stirred for 20 h at ambient temperature, followed by gradual neutralization with satd NaHCO₃ solution and extractions with CHCl₃ (3 × 20 mL). The CHCl₃ extracts were washed with water, dried (Na₂SO₄) and taken to dryness in vacuo. The syrupy residue crystallized on trituration with CH₂Cl₂/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 dihydroxypranone 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. (6S)-4-Benzoyloxy-6-methyl-2H-pyran-3(6H)-one 16

Pyridine (0.3 mL) was added to a solution of 15 (1.42 g, 4 mmol) in CHCl₃ (10 mL) and the mixture was heated for 5 min, followed by evaporation of dryness to vacuo. Crystallization of the residue from MeOH afforded 810 g (87%) of

5.16. 3,4-Di-O-benzoyl-1,5-anhydro-o-three-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-o-three-pent-1-enitol 24 (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 (Na₂SO₄) and recrystallized from CHCl₃/MeOH to give 9.4 g (75%) of colourless needles of mp 194–196 °C, which consisted of a 10:1 mixture of ²¹H NMR of the E-oxime 26 (Rᵣ = 0.56 in 10:1 CH₂Cl₂/EtOAc) and the respective Z-isomer (Rᵣ = 0.49).

A 500 mg sample was subjected to elution from a silica gel column (2 × 20 cm) with CH₂Cl₂/EtOAc 30:1; the first fractions containing 220 mg of the pure E-isomer; mp 198–199 °C; [α]D 25 = −111 (c 0.6, CHCl₃).²¹H NMR (500 MHz, CDCl₃): δ 3.89 and 4.13 (two 1H, 5-H₂), 4.85 and 4.67 (two 1H-d, 1-H₂), 5.37 (1H-dd, 1-H₂), 5.53 (1H-d, 3-H), 4.90 (1H-sx, 4-H), 5.18 (1H-d, 3-H), 11.48 (1H-s, NOH). J₁₁ = 14.1, J₁₂ = 5.0, J₁₃ = 3.1 and 5.0, J₁₄ = 12.2 Hz. Anal. Calc'd for C₁₀H₁₂NO₄ (231.20): C, 64.70; H, 5.59; N, 6.09.

5.17. 1,5-Anhydro-o-three-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 28 as fine prisms of mp 129.5–130.5 °C; [α]D20 = +14.8 (c 1, H2O). 1H NMR (300 MHz, DMSO-d6): 50.34 and 5.76 (two 1H-dd, 1-H2), 4.46 (1H-ddd, 5-He), 5.73 (1H-s, H-1), 5.18 (1H-d, 2-OH), 10.83 (1H-s, NOH); J1,1 = 13.8, J4,4 = 4.2, J5,5 = 2.2 and 3.6, J5,5 = 11.6 Hz. 13C NMR (75.47 MHz, DMSO-d6): δ 58.8 (C-1), 67.3 (C-5), 69.8 (C-3), 70.1 (C-4), 153.5 (C-2). Anal. Calcd for C176H16O6 (446.6): C, 45.45; H, 6.10. Found: C, 45.45; H, 6.06.

5.19.2. De-O-acetylation of 2-acetoxy-o-xyladecatetra 23

A methanolic solution of 23 (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-ProOH/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 1H and 13C NMR data with the product described above.

Desulfurization of dithioacetal by stirring an aqueous solution with CdCO3/HgCl2 as described for 10–2 and analogous workup similarly gave 4 in 75% yield.

5.20. 3,4-Di-O-benzoyl-1,5-anhydro-o-pentulose diethylidithioacetal 29

Ethanol (7.0 mL) and BF3 etherate (5 mL) were added to a suspension of pleuroside monohydrate 28 (12.9 g, 8.9 mmol) in CHCl3 (30 mL). The mixture was stirred for 5 min followed by dilution with CHCl3 (100 mL) and consecutive washings with 2 M NaOH and water (3 × 30 mL). Drying (Na2SO4) 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 (Rf = 0.57 in 2:1 cyclohexane/EtOAc) afforded 3.5 g (88%) of 29 as a colourless syrup; [α]D20 = −121.4 (c 0.8, CHCl3). 1H NMR (300 MHz, DMSO-d6): δ 1.10 and 1.24 (2H-ch, SET-Ch2); 2.70 (4H-m, SET-CH2); 3.72 and 4.21 (2H-1d, 5,5-H), 3.90 and 4.07 (2H-1d, 1-H2), 5.69 (1H-dd, dd, H-5), 5.80 (1H-3d, H-3); J1,1 = 12.6, J4,4 = 5.5 and 5.9 Hz, J5,5 = 10.5 Hz. 13C NMR (75.47 MHz, DMSO-d6): δ 14.1 and 14.2 (2 SET-Ch2), 22.4 and 22.5 (2 SET-Ch2), 62.1 (C-2), 67.2 (C-5), 69.1 (C-4), 72.1 (C-1), 76.0 (C-3). Anal. Calcd for C21H22O4S2 (466.6): C, 61.86; H, 5.87. Found: C, 61.76; H, 5.91.

5.21. 1,5-Anhydro-o-threo-pentulose diethylidithioacetal 30

To a cooled (0 °C) 0.1 M NaOMe/MeOH solution (100 mL) was added 5.5 g (123 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 syrup residue by elution from silica gel (25 × 30 cm column) with 20:1 CHCl3/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; [α]D20 = −79.3 (c 1.1, MeOH). 1H NMR (300 MHz, DMSO-d6): δ 1.13 and 1.14 (2H-ch, SET-Ch2); 2.72 (4H-m, SET-CH2); 3.02 (1H-1d, 4, H); 3.41 (1H-1d, 3-H); 3.46 and 3.76 (two 1H-1d, 1-H2); 3.80 (2H-4H, 5,5-H), 5.01 and 5.40 (two 1H-2d, 2 OH); J1,1 = 12.2, J4,4 = 8.1. 13C NMR (75.47 MHz, DMSO-d6): δ 14.2 and 14.4 (2 SET-Ch2), 21.8 and 22.6 (2 SET-Ch2), 64.1 (C-2), 67.7 (C-4), 71.1 (C-5), 73.3 (C-1), 79.8 (C-3). Anal. Calcd for C21H22O4S2 (384.4): C, 45.35; H, 7.61. Found: C, 45.18; H, 7.65.

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

A few drops of pyridine were added to a solution of 680 mg (2 mmol) of ulose dibenzoate 29 in CHCl3 (10 mL) and the mixture was heated at reflux for 10 min. Evaporation to dryness and recryst-
tallization of the residue from methanol gave 560 mg (82%) of 31 as colourless needles; mp 111–112 °C. 1H NMR (300 MHz, CDCl3): δ 4.32 (2H-s, 2-H2, 4.61 (1H-t, 5-H); J3,6 = 4.0 Hz. MS (FD): m/e = 218 (M+). Anal. Calcd for C12H17NO8 (303.26): C, 47.52; H, 5.65; N, 4.62. Found: C, 47.60; H, 5.60; N, 4.45.

3.4-6-Tri-O-acetyl-1,5-anhydro-o-sorbose E-oxime 35

A solution of hydroxylamine hydrochloride (250 mg) and of syrups 2-acetoxy-o-gulal triacetate 31,11 was stirred for 6 h at ambient temperature and subsequently poured into water (300 mL). Extraction with CHCl3 (3 × 50 mL) and consecutive washings of the combined extracts with 2 N HCl (3 × 50 mL), water (50 mL) and NaHCl3 solution (50 mL) and water (50 mL). Drying (Na2SO4) and evaporation to dryness in vacuo left 3.40 g (95%) of a solid residue which by 1H NMR proved to be a 4:1 mixture of E and Z isomers.

A mixture of hydroxylamine hydrochloride (2.50 g) and of syrup 2-acetoxy-cellobial hexa-acetate 31 was added 620 mg (1 mmol) of 2-acetoxy-cellobial hexa-acetate 31 and the mixture was stirred at ambient temperature for 7 h, subsequently diluted with water (10 mL) and extracted with CHCl3 (3 × 10 mL). The combined CHCl3 extracts were washed with water, dried (Na2SO4) and taken to dryness in vacuo. The syrup residue crystallized on trituration with ethanol: 430 mg (87%) of 37; mp 125–127 °C; [α]D27 = 22.3 (c 0.3, CHCl3). Rf = 0.31 (benzene/EtOAc 10:1). 1H NMR (300 MHz, DMSO-d6): δ = 1.99, 2.01 and 2.03 (3s, 18H, 6 Ac-C; J1,1 = 3.2 Hz). 13C NMR (75.47 MHz, DMSO-d6): δ = 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 = 218 (M+). Anal. Calcd for C12H10O4 (218.2): C, 66.05; H, 4.54; N, 2.83. Found: C, 66.01; H, 4.54.

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References

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