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Inhibition of the D-fructose transporter protein GLUT5 by fused-ring glyco-1,3-oxazolidin-2-thiones and -oxazolidin-2-ones

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Abstract

The glucose transporter 5 (GLUT5)—a specific D-fructose transporter—belongs to a family of facilitating sugar transporters recently enlarged by the human genome sequencing. Prompted by the need to develop specific photolabels of these isoforms, we have studied the interaction of conformationally locked D-fructose and L-sorbose derived 1,3-oxazolidin-2-thiones and 1,3-oxazolidin-2-ones to provide a rational basis for an interaction model. The inhibition properties of the D-fructose transporter GLUT5 by glyco-1,3-oxazolidin-2-thiones and glyco-1,3-oxazolidin-2-ones is now reported. In vitro, the fused-rings systems tested showed an efficient inhibition of GLUT5, thus bringing new insights on the interaction of D-fructose with GLUT5.

Keywords: 1,3-Oxazolidine-2-one; 1,3-Oxazolidine-2-thione; D-Fructose; L-Sorbose; GLUT5

1. Introduction

Recent human genome sequencing has led to realize that the family of facilitating sugar transporters (GLUTs: glucose transporters) in mammals is more extensive than the group of five members (GLUTs 1–5) described a decade ago. Now the GLUTs are known to be a more complex family of 13 isomeric proteins that is divisible into three sub-groups based on sequence similarities.[1] The class A group consists of the glucose transporters (GLUTs 1–4) which preferentially transport D-glucose. The class B group includes GLUT5 and several similar isoforms. GLUT5 is known to be specific for D-fructose and it has therefore been assumed (based on sequence similarity) that GLUT7 and GLUT9 have similar specificity. GLUT8 and GLUT10 transport both D-glucose and D-fructose[2–4] and are members of the third class C sub-group of transporters which also includes the uncharacterised GLUT12. However, a member of the class C sub-group is specific for myo-inositol.[5]

An improved characterisation of the GLUTs will require a more complete analysis of interaction with D-glucose and D-fructose analogues that define the specificities and functions of these isoforms. A range of D-glucose analogues has been used to define the analogue specificities of the class A sub-group[6–9] but the analysis of the class B (D-fructose specific) and class C (D-glucose and D-fructose specific) sub-groups requires the development of a new range of analogues and potentially isoform-specific inhibitors. The sugar transporters of trypanosomes and plasmodium also facilitate uptake of both D-glucose and D-fructose.[10,11] Design of anti-parasitic reagents based on selective inhibition of these transporters, excluding those of the mammalian hosts,[12,13] will require detailed comparisons of the binding site specificity.

For initial development and analysis of D-fructose analogues, we have utilised a system in which GLUT5 is expressed in Chinese Hamster Ovary (CHO) cells.[14,15]

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We have previously found that a major difficulty in analysis of D-fructose interactions with its transporters is its ability to exist in α,β-pyranose or α,β-furanose forms (Fig. 1). By using both D-fructofuranoside and D-fructopyranoside analogues as inhibitors of D-fructose transport in CHO-GLUT5 cells, we have been able to establish that both ring forms are tolerated.

However, L-sorbose, which is predominantly present in solution in the pyranose form, is not well recognized. We now consider that these interactions may occur because D-fructofuranose is a relatively symmetrical molecule and can be recognized by the binding site on either face: the anomeric center leading (top middle panel, Fig. 1) or the anomeric center trailing (top right panel, Fig. 1). D-Fructopyranose (but not L-sorbopyranose) may offer similar hydrogen bonding groups to the transporter (left panels).

Of a large range of *O*-allyl substituted D-fructoses, only 6-*O*-allyl-D-fructofuranose is well recognized, suggesting that this molecule adopts a position in the binding site in which C-6 is trailing (top middle panel, Fig. 1). However, other D-fructose derivatives which are also well recognized, such as 1,2-*O*-isopropylidene-β-D-fructopyranose, may adopt a conformation in which C-1 and C-2 are trailing (top left panels, Fig. 1). Conformationally restricting the number of ring conformations was considered to be important in the development of new analogues with large substituted groups. In addition, we wished to explore the possibility that L-sorbose analogues (in contrast to L-sorbose itself) might be good inhibitors if they could be locked into a furanose ring form.

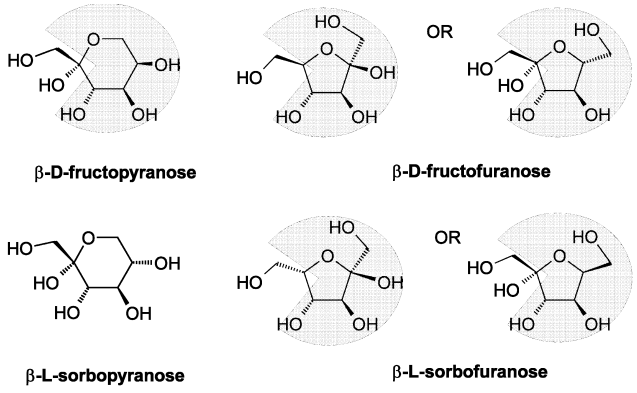
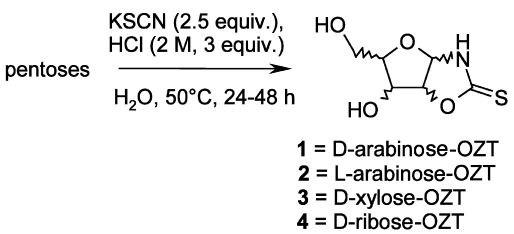


Fig. 1. D-Fructose and L-sorbose in pyranose and furanose forms and proposed orientation in relation to the GLUT5 binding site (shaded) residues. The furanose form of D-fructose is more symmetrical than the pyranose form and it is proposed that the furanose-form can occupy positions in the binding site (shaded) either with the anomeric center leading (top-middle panel) or trailing (top-right panel). In order to tolerate bulky substitutions at the anomeric center, the latter binding-site-occupancy state may occur. The pyranose form of D-fructose may be restricted to occupying the site with the anomeric center trailing (top-left panel). By contrast, L-sorbopyranose is not well tolerated but we explore in this study whether its furanose-derivatives may be good inhibitors (bottom panels).



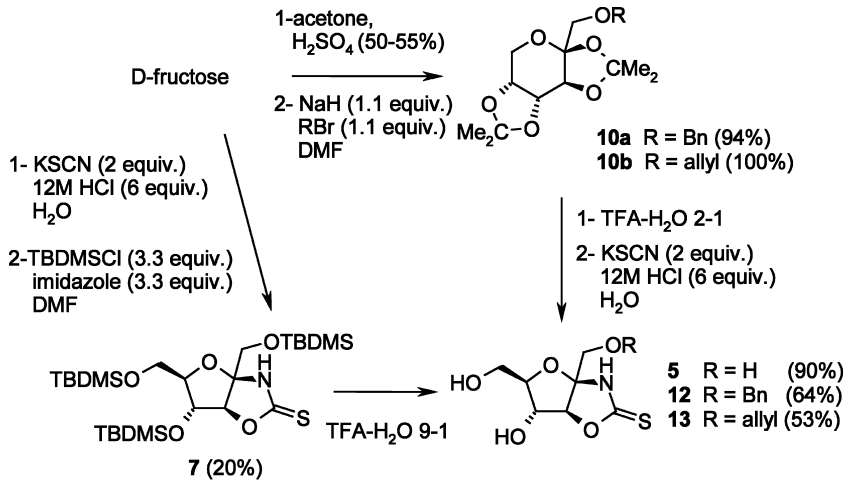
Scheme 1. Synthesis of oxazolidinethiones derived from pentoses.

2. Results and discussion

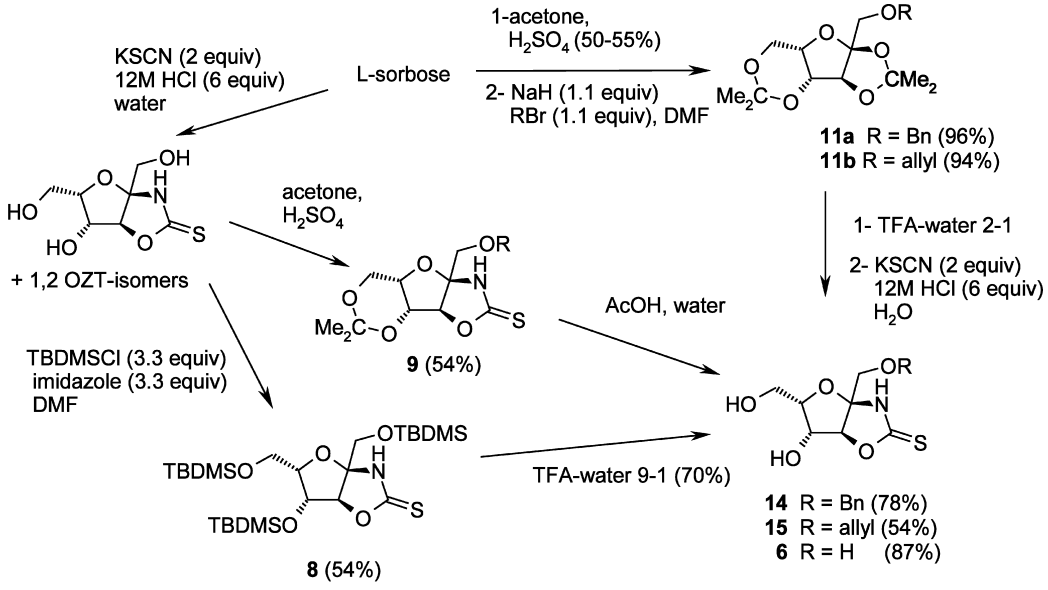
We address these issues here by studying the properties of a new series of conformationally locked carbohydrates in which a fused furanose ring is established by formation of 1,3-oxazolidin-2-thione (OZT) or 1,3-oxazolidin-2-one (OZO) derivatives. The simplest OZT aldopentose fused ring systems **1**–**4** (Scheme 1) are usually prepared in a single step, using potassium thiocyanate under acidic conditions with fair to good yields and high specificity for the furanose ring.[16] Attempts to attain the same selectivity and yields from the ketohexoses were not as successful and, due to purification problems between possible OZT isomers, a three steps sequence was required to obtain pure OZT derivatives **5** and **6**[17] (Schemes 2 and 3). After usual processing, yielding mixtures of OZT isomers, silylation of the crude product afforded separable mixtures on column chromatography. Silylated products **7** and **8** were isolated in moderate yields, respectively 20 and 54% in a two step-process. Acidic deprotections lead to pure OZT derivatives **5** and **6** in, respectively 90 and 70% yields. A more efficient and less expensive approach was developed to synthesize L-sorbose OZT **6** using a 4,6-*O*-isopropylidene protection leading to **9** (with a similar yield as for **7**), followed by a smooth deprotection in AcOH–water to afford **6** in 87% yield.

In order to get the 1-*O* substituted derivatives **12**–**15** (Schemes 2 and 3), a four-step sequence was used. The first two steps involved acetonation of both D-fructose and L-sorbose followed by either standard *O*-benzylation of the primary alcohol group to obtain **10a** and **11a**, or *O*-allylation to **10b** and **11b** in reasonable yields.

Hydrolysis of the isopropylidene groups under acidic conditions (trifluoroacetic acid) then application of the efficient OZT preparation procedure led to the target D-fructose **12** and **13** (Scheme 2) and L-sorbose derivatives **14** and **15** (Scheme 3). In all cases only one furanose anomeric form of OZT was detected and isolated.



Scheme 2. Oxazolidinethiones derived from D-fructose.

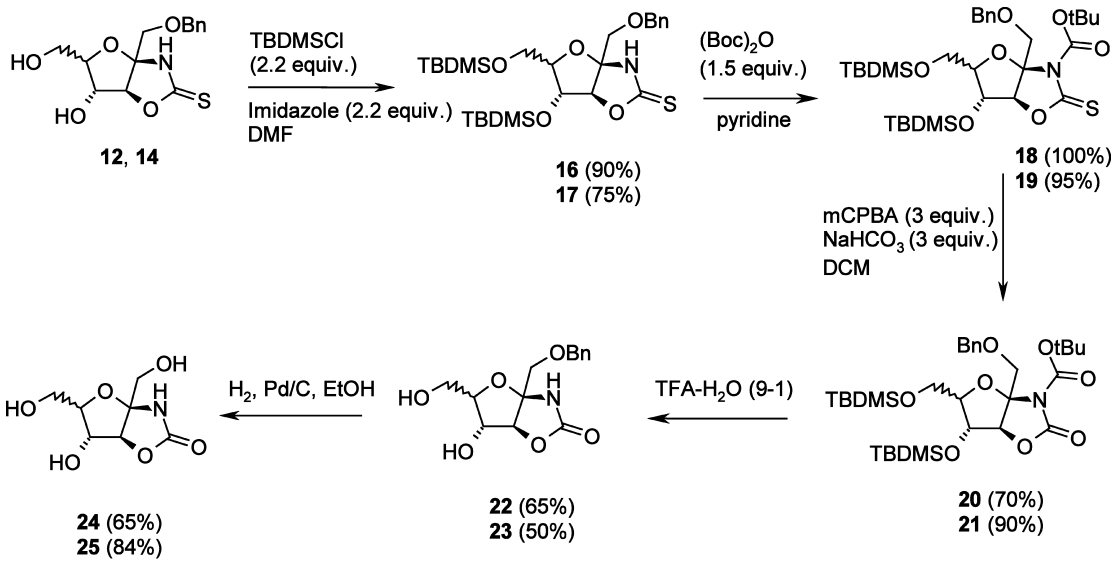


Scheme 3. Synthesis of oxazolidinethiones derived from L-sorbose.

We initially planned access to OZO **22**–**25** (Scheme 4) by reacting 1-*O*-alkyl ketoses with potassium cyanate, which would produce the desired products.[18] Quite unexpectedly, the yields observed were rather low and not reproducible. Therefore, having in hand the readily obtained OZT compounds, we decided to convert them into the corresponding OZO derivatives. We found that a direct conversion of OZT derivatives **12**, **14** to OZO derivatives **22**, **23** by oxidation was not possible, so that a multi-step process was needed (Scheme 4). Keeping in mind the oxidation route, silyl ether protection of the hydroxyls in OZT **12**, **14** to afford **16**, **17**, then BOC protection of the thionocarbamate function to **18**, **19** was carried out. At this stage, oxidation was undertaken to produce in reasonable yields OZO **20**, **21**. The final acidic hydrolysis of all protecting groups afforded good yields of the 1-*O*-benzylated OZO **22** and **23**, which were submitted to hydrogenolysis under standard conditions leading to OZO derivatives **24** and **25**.[18]

Considering the results obtained by analysing the ability of the 14 OZT and OZO compounds to inhibit D-fructose transport (Table 1), several important conclusions have been reached regarding the specificity of GLUT5.

The half-maximal inhibition (K_i) values of the OZT derived pentoses **1**–**4** are >90 mM. Values in this range indicate that no significant inhibition of D-fructose transport has occurred. However, when the K_i values of the pentoses are compared with the K_i value for D-fructose-OZT (**5**; $K_i = 25$ mM), the importance of the C-1 hydroxymethyl group of D-fructose is evident (as this carbon site is absent in the pentose derivatives). This is particularly the case for the D-arabinose deriva-



Scheme 4. Synthesis of D-fructose and L-sorbose derived oxazolidinones.

tive as the configuration of the C-1 to C-4 hydroxyls is the same as in D-fructose. Moreover, comparisons between D-fructose-OZT compounds (**5**, **12**, **13**) and the equivalent L-sorbose-OZT derivatives (**6**, **14**, **15**) in which the C-5 hydroxymethyl group has the opposite configuration, indicate a better inhibition constant for the latter derivatives. In addition, these results indicate that if L-sorbose analogues can be forced to adopt a furanose ring form, then these are well recognized (in contrast to L-sorbose itself, which is predominately in the pyranose ring form).

The benzyl and allyl derivatives of both D-fructose and L-sorbose have higher affinity than the C-1-unsubstituted compounds. Consideration of the ways in which the binding site could tolerate the bulky benzyl and allyl groups, supports our hypothesis. Bulky part of the furanose derivatives may occupy a position out of the binding site. Thus, the C-6 hydroxymethyl group of L-sorbose may occupy the position normally occupied by C-1 of β-D-fructofuranose (Fig. 1, top-middle panel). In that way the C-1 bulky groups may occupy an opening in the binding-site cleft in which steric constraints are less critical (Fig. 1, right panels).

Finally, replacing sulfur by oxygen from an OZT to an OZO derivative, leads to more potent inhibitors by factors of 2–4 especially for derivative **23** ($K_i = 3.1$ mM) which is the best inhibitor of this study. Sulfur thus appears to hamper the association by possibly lowering some hydrogen interaction with the protein.[15]

In summary from these studies, it appears that locked conformations of ketofuranoses provide better interacting molecules (by factor 6) with D-fructose transporter GLUT5 than those previously reported.[14] In view of our previous studies and the present one, the proposed interaction model of D-fructose with GLUT5 (Fig. 1) seems fairly consistent. Further structural studies on fructopyranose locked conformations and functional modifications of the best inhibitor **23** are under investigations with a view to develop more efficient inhibitors and biochemical tools.

Table 1
Interaction of the OZT and OZO derived sugars with the GLUT5 transporter

Compound	Derivative type	K_i (mM)
	D-fructose	15.5 ± 2.9
1	D-arabinose-OZT	104.5 ± 21.3
2	L-arabinose-OZT	122.8 ± 27.6
3	D-xylose-OZT	106.2 ± 27.1
4	D-ribose-OZT	109.9 ± 24.3
12	D-fructose-Bn-OZT	32.6 ± 3.6
13	D-fructose-allyl-OZT	20.8 ± 3.8
5	D-fructose-OZT	24.9 ± 3.2
14	L-sorbose-Bn-OZT	12.4 ± 1.5
15	L-sorbose-allyl-OZT	14.5 ± 2.1
6	L-sorbose-OZT	17.4 ± 6.7
22	D-fructose-Bn-OZO	8.5 ± 1.7
24	D-fructose-OZO	11.9 ± 3.4
23	L-sorbose-Bn-OZO	3.1 ± 0.5
25	L-sorbose-OZO	7.2 ± 1.0

Uptake of 1 mM [^{14}C]-D-fructose into CHO cells expressing GLUT5 was measured at a range of D-fructose concentrations (usually serial increases in concentration up to 40 mM). The K_i values were calculated by least squares fitting to the equation $V_o/V = 1 + I/K_i$ (where V_o and V are the D-fructose uptake rate constants in the absence and presence of inhibitor, respectively). The tabulated values are the mean and S.E.M. of 3–5 independent experiments.[7]

3. Experimental

3.1. General methods

Melting points were determined on a Büchi 510 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively (Bruker Avance DPX-250 instrument) in $CDCl_3$ (unless otherwise stated) with Me_4Si as internal standard; for other solvents, the residual peak was used as internal standard. Whenever appropriate, signal assignments were deduced by DEPT, COSY and HETCOR NMR experiments. Optical rotations were measured at 20 °C on a Perkin–Elmer 141 polarimeter using a sodium lamp. Low resolution mass spectra (MS) were recorded by the ICOA Analytical Service on a Perkin–Elmer SCIEX API 300 (ISMS). Elemental analysis was performed by the micro-analysis service at the University of Bath and by the analytical service of the CNRS, Vernaison. Analytical TLC was carried out on precoated Silica Gel 60F-254 plates (E. Merck) and spots were visualised by UV light (254 nm) and developed by charring after a 5% H_2SO_4 ethanolic solution spray. Column chromatography was performed on Silica Gel SI 60 (43–60 μm) (E. Merck) either with petroleum ether–EtOAc mixtures (19:1 eluent A, 1–1 B, 2–8 C) or with eluent D: 4:1 EtOAc–MeOH.

3.2. General protocol for the synthesis of silylated OZT derivatives 7 and 8 from D-fructose and L-sorbose

The ketose (1 equiv) was suspended in water (0.5 M) then KSCN (2.05 equiv) and 12 N HCl 37% (2.2 equiv) were added. The pink solution obtained was warmed up to 50 °C for 5 days. Water was removed by co-evaporation with toluene and the crude mixture suspended in acetone. Salts were removed and the solvent evaporated. The dry crude mixture was silylated with TBDMSCl (33 mmol) and imidazole (33 mmol) in DMF (50 mL) at room temperature (rt) for 48 h. Extraction with EtOAc was conducted twice, the organic layers were collected and washed with water $\times 5$ then brine, and dried with $MgSO_4$. The resulting mixture was concentrated under diminished pressure then purified by column chromatography using eluent A, yielding **7** and **8**, respectively.

3.3. 1,4,6-Tri-*O*-*tert*-butyldimethylsilyl-2-*N*,3-*O*-thiocarbonyl-β-D-fructofuranosylamine (7)

White powder (1.3 g, 20%); $[\alpha]_D^{20}$ −19° (*c* 0.5, MeOH); ^{1}H NMR: δ 7.18 (s broad, 1 H, NH), 4.83 (s, 1 H, H-3), 4.51 (s, 1 H, H-4), 4.13–4.04 (m, 1 H, H-5), 3.82 (d, 1 H, $J_{1a,1b}$ 10.9 Hz, H-1a), 3.73 (d, 1 H, H-1b), 3.64 (dd, 1 H, $J_{6a,5}$ 5.3, $J_{6a,6b}$ 10.7 Hz, H-6a), 3.64 (dd, 1 H, $J_{6b,5}$ 8.9, H-6b), 0.88 (s, 27 H, CH_3), 0.13, 0.11, 0.07 and 0.06 (4s, 18 H, CH_3Si); ^{13}C NMR: δ 188.8 (CS), 100.9 (C-2), 93.1 (C-3), 88.6 (C-5), 76.1 (C-4), 63.8 (C-1), 62.2 (C-6), 26.0 (CH_3), 25.9 (CH_3), 25.7 (CH_3), 18.4 (CMe_3), 18.0 (CMe_3), −4.3 and −4.7 (CH_3Si); ISMS (+): *m*/*z* 564.5 $[M+H]^+$, 586.5 $[M+Na]^+$. Anal. Calcd for $C_{25}H_{53}NO_5SSi_3$: C, 53.24; H, 9.47; N, 2.48. Found: C, 53.02; H, 9.52; N, 2.55.

3.4. 1,4,6-Tri-*O*-*tert*-butyldimethylsilyl-2-*N*,3-*O*-thiocarbonyl-α-L-sorbofuranosylamine (8)

White powder (3.0 g, 54%); mp: 145–148 °C; $[\alpha]_D^{20}$ −16° (*c* 1.1, MeOH); ^{1}H NMR: δ 7.28 (s broad, 1 H, NH), 4.75 (s, 1 H, H-3), 4.38 (d, 1 H, $J_{4,5}$ 2.5 Hz, H-4), 4.03 (ddd, 1 H, $J_{5,6a}$ 6.0, $J_{5,6b}$ 6.6 Hz, H-5), 3.84 (d, 1 H, $J_{1a,1b}$ 11.0 Hz, H-1a), 3.80 (dd, 1 H, $J_{6a,6b}$ 10.4 Hz, H-6a), 3.73 (dd, 1 H, H-6b), 3.71 (d, 1 H, H-1b), 0.89 and 0.88 (s, 27 H, CH_3), 0.13, 0.11, 0.07, 0.06, and 0.05 (5s, 18 H, CH_3Si); ^{13}C NMR: δ 189.2 (CS), 100.2 (C-2), 91.3 (C-3), 82.3 (C-5), 73.9 (C-4), 63.7 (C-1), 60.0 (C-6), 26.0 (CH_3), 25.9 (CH_3), 25.7 (CH_3), 18.5 (CMe_3), 18.3 (CMe_3), −4.7, −5.1 and −5.4 (CH_3Si); ISMS (+): *m*/*z* 564.5 $[M+H]^+$, 586.5 $[M+Na]^+$. Anal. Calcd for $C_{25}H_{53}NO_5SSi_3$: C, 53.24; H, 9.47; N, 2.48. Found: C, 52.82; H, 9.49; N, 2.42.

3.5. 4,6-*O*-Isopropylidene-2-*N*,3-*O*-thiocarbonyl-α-L-sorbofuranosylamine (9)

The crude mixture obtained from L-sorbose (1.66 g, 8 mmol) under the general protocol for OZT formation (**7** and **8**) was diluted in dry acetone (50 mL), cooled in an ice bath and concd H_2SO_4 (95%, 0.3 mL) was added. After 24 h at rt, the mixture was made neutral with Et_3N, the solvent removed and the residue purified on silica gel (eluent B), yielding **9** as a pale yellow foam (1.3 g, 54%) was obtained; $[\alpha]_D^{20}$ −73° (*c* 2, MeOH); ^{1}H NMR: δ 7.94 (s broad, 1 H, NH), 4.95 (s, 1 H, H-3), 4.55 (d, 1 H, $J_{4,5}$ 2.1 Hz, H-4), 4.20–3.98 (m, 4 H, H-6, H-1a, H-5), 3.88 (dd, 1 H, $J_{1a,1b}$ 11.6 Hz, H-1b), 2.97 (s broad, 1 H, OH), 1.47 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3); ^{13}C NMR: δ 189.1 (CS), 100.4 (CMe_2), 98.4 (C-2), 90.4 (C-3), 72.4 (C-4), 72.1 (C-5), 62.9 (C-1), 59.5 (C-6); ISMS (+): *m*/*z* 262 $[M+H]^+$. Anal. Calcd for $C_{10}H_{15}NO_5S$: C, 45.97; H, 5.79; N, 5.36. Found: C, 46.23; H, 6.10; N, 5.41.

3.6. General protocol for the synthesis of OZT derivatives 5 and 6

Deprotection of silyl groups in **7** and **8** was effected at 0.3 M in 9:1 TFA–water for 24 h. Acetal deprotection of **9** was effected in 4:1 AcOH–water. Solvent were removed by co-evaporation with MeOH or toluene and the crude product purified by flash chromatography with EtOAc, yielding **5** and **6**, respectively.

3.7. 2-*N*,3-*O*-Thiocarbonyl-β-D-fructofuranosylamine (5)

(0.17 g, 90%); $[\alpha]_D^{20}$ −10° (*c* 1, MeOH); ^{1}H NMR (CD_3OD): δ 4.98 (d, 1 H, $J_{3,4}$ 1.3 Hz, H-3), 4.36 (dd, 1 H, $J_{4,5}$ 2.5 Hz, H-4), 4.10 (dt, 1 H, $J_{5,6}$ 6.5 Hz, H-5), 3.78 (d, 1 H, $J_{1a,1b}$ 11.9 Hz, H-1a), 3.69 (d, 1 H, H-1b), 3.53 (d, 2 H, H-6); ^{13}C NMR (CD_3OD): δ 190.5 (CS), 102.5 (C-2), 93.5 (C-3), 88.8 (C-5), 76.8 (C-4), 62.9 (C-1), 62.6 (C-6); ISMS (+): *m*/*z* 222 $[M+H]^+$. Anal. Calcd for $C_7H_{11}NO_5S$: C, 38.00; H, 5.01; N, 6.33. Found: C, 38.05; H, 5.05; N, 6.18.

3.8. 2-*N*,3-*O*-Thiocarbonyl-α-L-sorbofuranosylamine (6)

(0.19 g, 70%) from **8** and (0.20 g, 87%) from **9**; $[\alpha]_D^{20}$ −22° (*c* 1.1, MeOH); ^{1}H NMR (CD_3OD): δ 4.91 (s, 1 H, H-3), 4.31 (d, 1 H, $J_{4,5}$ 2.8 Hz, H-4), 3.99–3.94 (m, 1 H, H-5), 3.90–3.78 (m, 3 H, H-6, H-1a), 3.70 (d, 1 H, $J_{1a,1b}$ 11.9 Hz, H-1b); ^{13}C NMR (CD_3OD): δ 190.9 (CS), 101.7 (C-2), 92.0 (C-3), 82.6 (C-5), 74.8 (C-4), 62.7 (C-1), 60.4 (C-6); ISMS (+): *m*/*z* 222 $[M+H]^+$. Anal. Calcd for $C_7H_{11}NO_5$: C, 38.00; H, 5.01; N, 6.33. Found: C, 38.29; H, 5.21; N, 6.23.

3.9. General protocol for the synthesis of 1,3-oxazolidine-2-thiones 12–15 from 1-*O*-alkylated ketoses

The 1-*O*-alkylated ketose (1 equiv) was suspended in water (0.08 M), then KSCN (2.05 equiv) and 12 N HCl (2.4 equiv) were added. The pink solution obtained was maintained at 50 °C during 48 h. Water was removed by co-evaporation with toluene and the crude mixture purified by column chromatography (eluent C), yielding **12**–**15**.

3.10. 1-*O*-Benzyl-2-*N*,3-*O*-thiocarbonyl-β-D-fructofuranosylamine (12)

Yellow foam (0.62 g, 100%); $[\alpha]_D^{20}$ −24° (*c* 2, MeOH); ^{1}H NMR (Me_2SO–D_2O): δ 7.48–7.23 (m, 5 H, Ph–H), 4.87 (d, 1 H, $J_{3,4}$ 0.9 Hz, H-3), 4.60 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.55 (d, 1 H, CH_2Ph), 4.25 (s, 1 H, H-4), 3.93 (ddd, 1 H, $J_{5,4}$ 2.5 Hz, H-5), 3.66 (d, 1 H, $J_{1a,1b}$ 10.4 Hz, H-1a), 3.56 (d, 1 H, H-1b), 3.37 (dd, 1 H, $J_{5,6a}$ 6.3, $J_{6a,6b}$ 11.3 Hz, H-6a), 3.30 (dd, 1 H, H-6b); ^{13}C NMR (Me_2SO): δ 187.7 (CS), 137.7 (C), 128.4 (CH), 127.8 (CH), 127.6 (CH), 99.5 (C-2), 91.8 (C-3), 87.1 (C-5), 74.9 (C-4), 72.6 (CH_2), 69.3 (C-1), 60.7 (C-6); ISMS (+): *m*/*z* 312.5 $[M+H]^+$, 334.5 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{17}NO_5S$: C, 54.01; H, 5.50. Found: C, 53.62; H, 5.52.

3.11. 1-*O*-Allyl-2-*N*,3-*O*-thiocarbonyl-β-D-fructofuranosylamine (13)

Pale yellow foam (2.5 g, 100%); $[\alpha]_D^{20}$ −39° (*c* 1, MeOH); ^{1}H NMR (CD_3OD): δ 5.91 (ddt, 1 H, $J_{\beta,\alpha}$ 5.7, $J_{\beta,\gamma Z}$ 11.3, $J_{\beta,\gamma E}$ 17.3 Hz, H-β_{allyl}), 5.36–5.14 (m, 2 H, H-γ_{allyl}), 4.94 (d, 1 H, $J_{3,4}$ 1.3 Hz, H-3), 4.35 (dd, 1 H, $J_{4,5}$ 2.5 Hz, H-4), 4.12–4.04 (m, 3 H, H-5, Hα_{allyl}), 3.70 (d, 1 H, $J_{1a,1b}$ 10.4 Hz, H-1a), 3.62 (d, 1 H, H-1b), 3.52 (d, 2 H, $J_{5,6}$ 6.6 Hz, H-6); ^{13}C NMR (67.5 MHz, Me_2SO): δ 190.4 (CS), 135.4 (Cβ), 117.8 (Cγ), 101.2 (C-2), 93.8 (C-3), 88.7 (C-5), 76.7 (C-4), 73.4 (Cα), 70.5 (C-1), 62.5 (C-6); ISMS (+): *m*/*z* 262 $[M+H]^+$, 284 $[M+Na]^+$. Anal. Calcd for $C_{10}H_{15}NO_5S$: C, 45.97; H, 5.79. Found: C, 46.10; H, 5.94.

3.12. 1-*O*-Benzyl-2-*N*,3-*O*-thiocarbonyl-α-L-sorbofuranosylamine (14)

Yellow foam (1.8 g, 74%); $[\alpha]_D^{20}$ −30° (*c* 2, MeOH); ^{1}H NMR (Me_2SO–D_2O): δ 10.85 (s broad, 1 H, NH), 7.48–7.21 (m, 5 H, Ph–H), 4.81 (s, 1 H, H-3), 4.60 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.55 (d, 1 H, CH_2Ph), 4.18 (d, 1 H, $J_{4,5}$ 2.5 Hz, H-4), 3.76 (ddd, 1 H, $J_{5,6a}$ 4.7, $J_{5,6b}$ 6.2 Hz, H-5), 3.69 (d, 1 H, $J_{1a,1b}$ 10.4 Hz, H-1a), 3.66 (dd, 1 H, $J_{6a,6b}$ 11.6 Hz, H-6a), 3.56 (d, 1 H, H-1b), 3.53 (dd, 1 H, H-6b); ^{13}C NMR (Me_2SO): δ 188.0 (CS), 137.7 (C), 128.4 (CH), 127.7 (CH), 127.6 (CH), 99.0 (C-2), 90.2 (C-3), 81.5 (C-5), 72.72 (CH_2), 72.6 (C-4), 69.1 (C-1), 58.4 (C-6); ISMS (+): *m*/*z* 312.5 $[M+H]^+$, 334.5 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{17}NO_5S$: C, 54.01; H, 5.50. Found: C, 54.03; H, 5.63.

3.13. 1-*O*-Allyl-2-*N*,3-*O*-thiocarbonyl-α-L-sorbofuranosylamine (15)

Yellow foam (3.9 g, 75%); $[\alpha]_D^{20}$ −29° (*c* 1, MeOH); ^{1}H NMR (CD_3OD): δ 5.91 (ddt, 1 H, $J_{\beta,\alpha}$ 5.7, $J_{\beta,\gamma Z}$ 11.0, $J_{\beta,\gamma E}$ 17.3 Hz, H-β_{allyl}), 5.36–5.15 (m, 2 H, H-γ_{allyl}), 4.88 (s, 1 H, H-3), 4.31 (d, 1 H, $J_{4,5}$ 2.8 Hz, H-4), 4.12–4.05 (m, 2 H, Hα_{allyl}), 3.95 (ddd, 1 H, $J_{5,6a}$ 4.7, $J_{5,6b}$ 6.6 Hz, H-5), 3.85 (dd, 2 H, $J_{6a,6b}$ 11.9 Hz, H-6), 3.76 (dd, 2 H, H-6), 3.73 (d, 1 H, $J_{1a,1b}$ 10.7 Hz, H-1a), 3.64 (d, 1 H, H-1b); ^{13}C NMR (Me_2SO): δ 190.8 (CS), 135.4 (Cβ), 117.8 (Cγ), 100.6 (C-2), 92.4 (C-3), 82.7 (C-5), 74.8 (C-4), 73.5 (Cα), 70.4 (C-1), 60.4 (C-6); ISMS (+): *m*/*z* 262 $[M+H]^+$. Anal. Calcd for $C_{10}H_{15}NO_5S$: C, 45.97; H, 5.79. Found: C, 46.02; H, 5.89.

3.14. General protocol for the preparation of silylated 16 and 17

The OZT (1 equiv), imidazole (5 equiv) and TBDMSCl (2.5 equiv) were dissolved in DMF (10 mL) and the mixture stirred overnight at rt. After completion, water was added and the resulting solution was extracted twice with CH_2Cl_2. Collected organic layers were washed abundantly with water then once with brine and subsequently dried with $MgSO_4$ and evaporated. A short column chromatography (eluent A) afforded the protected OZT derivatives **16** and **17**.

3.15. 1-*O*-Benzyl-4,6-di-*O*-*tert*-butyldimethylsilyl-2-*N*,3-*O*-thiocarbonyl-β-D-fructofuranosylamine (16)

Yellow oil (1.8 g, 100%); $[\alpha]_D^{20}$ −55° (*c* 2, MeOH); ^{1}H NMR: δ 8.55 (s broad, 1 H, NH), 7.28–7.12 (m, 5 H, Ph–H), 4.74 (s, 1 H, H-3), 4.52 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.47–4.38 (m, 2 H, H-4, CH_2Ph), 4.05–3.94 (m, 1 H, H-5), 3.59 (d, 1 H, $J_{1a,1b}$ 10.4 Hz, H-1a), 3.56 (dd, 1 H, $J_{5,6a}$ 5.3, $J_{6a,6b}$ 10.4 Hz, H-6a), 3.49 (d, 1 H, H-1b), 3.37 (ft, 1 H, H-6b), 0.79 (s, 9 H, CH_3), 0.76 (s, 9 H, CH_3), 0.01, 0.00, −0.01 and −0.03 (4s, 12 H, CH_3Si); ^{13}C NMR: δ 188.4 (CS), 137.0 (C), 128.5 (CH), 128.0 (CH), 127.8 (CH), 100.0 (C-2), 92.9 (C-3), 88.4 (C-5), 75.9 (C-4), 73.6 (CH_2), 69.5 (C-1), 61.9 (C-6), 25.9 (CH_3), 25.6 (CH_3), 18.2 (CMe_3), 17.8 (CMe_3), −5.0, −5.3, −5.4 (CH_3Si); ISMS (+): *m*/*z* 540.5 $[M+H]^+$, 562 $[M+Na]^+$. Anal. Calcd for $C_{26}H_{45}NO_5SSi_2$: C, 57.84; H, 8.40; N, 2.59. Found: C, 57.61; H, 8.59; N, 2.49.

3.16. 1-*O*-Benzyl-4,6-di-*O*-*tert*-butyldimethylsilyl-2-*N*,3-*O*-thiocarbonyl-α-L-sorbofuranosylamine (17)

Yellow oil (3.1 g, 85%); $[\alpha]_D^{20}$ −21° (*c* 2, MeOH); ^{1}H NMR: δ 7.51 (s broad, 1 H, NH), 7.39–7.24 (m, 5 H, Ph–H), 4.76 (s, 1 H, H-3), 4.62 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.52 (d, 1 H, CH_2Ph), 4.38 (d, 1 H, $J_{4,5}$ 2.5 Hz, H-4), 4.02 (ddd, 1 H, $J_{5,6a}$ 5.9, $J_{5,6b}$ 6.6, $J_{6a,6b}$ 10.0 Hz, H-5), 3.80 (dd, 1 H, H-6a), 3.74 (dd, 1 H, H-6b), 3.69 (d, 1 H, $J_{1a,1b}$ 10.4 Hz, H-1a), 3.58 (d, 1 H, H-1b), 0.87 (s, 9 H, CH_3), 0.84 (s, 9 H, CH_3), 0.09, 0.05 and 0.04 (3s, 12 H, CH_3Si); ^{13}C NMR: δ 188.9 (CS), 137.0 (C), 128.6 (CH), 128.2 (CH), 128.0 (CH), 99.1 (C-2), 91.4 (C-3), 82.0 (C-5), 73.9 (CH_2), 73.8 (C-4), 69.6 (C-1), 59.7 (C-6), 26.0 (CH_3), 25.7 (CH_3), 18.4 (CMe_3), 18.0 (CMe_3), −4.8, −5.2, −5.3 (CH_3Si); ISMS (+): *m*/*z* 540.5 $[M+H]^+$. Anal. Calcd for $C_{26}H_{45}NO_5SSi_2$: C, 57.84; H, 8.40; N, 2.59. Found: C, 57.59; H, 8.46; N, 2.40.

3.17. General protocol for preparation of the *tert*-butoxycarbonyl derivatives 18 and 19

The above OZT (1 equiv) was reacted with Boc_2O (1.5 equiv) in dry Py (0.3 M) for 24 h at rt. After concentration under diminished pressure, the crude mixture was purified by flash column chromatography (eluent A).

3.18. 1-*O*-Benzyl-2-*N*-*tert*-butoxycarbonyl-4,6-di-*O*-*tert*-butyldimethylsilyl-2-*N*,3-*O*-thiocarbonyl-β-D-fructofuranosylamine (18)

Yellow oil (0.68 g, 100%); $[\alpha]_D^{20}$ −15° (*c* 2, MeOH); ^{1}H NMR: δ 7.38–7.24 (m, 5 H, Ph–H), 4.76 (s, 1 H, H-3), 4.59 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.54–4.46 (m, 2 H, H-4, CH_2Ph), 4.18 (d, 1 H, $J_{1a,1b}$ 9.7 Hz, H-1a), 4.14–4.05 (m, 1 H, H-5), 3.62 (d, 1 H, H-1b), 3.61 (dd, 1 H, $J_{5,6a}$ 4.4, $J_{6a,6b}$ 10.7 Hz, H-6a), 3.42 (dd, 1 H, $J_{5,6b}$ 8.8 Hz, H-6b), 1.52 (s, 9 H, CH_3), 0.87 (s, 9 H, CH_3), 0.85 (s, 9 H, CH_3), 0.09, 0.08 and 0.04 (3s, 12 H, CH_3Si); ^{13}C NMR: δ 184.0 (CS), 148.9 (CO), 137.1 (C), 128.6 (CH), 128.1 (CH), 127.8 (CH), 101.9 (C-2), 90.5 (C-3), 89.1 (C-5), 85.1 (CMe_3), 76.0 (C-4), 73.5 (CH_2), 68.9 (C-1), 62.0 (C-6), 27.9 (CH_3), 25.9 (CH_3), 25.7 (CH_3), 18.2 (CMe_3), 17.9 (CMe_3), −4.9, −5.2, −5.3 (CH_3Si); ISMS (+): *m*/*z* 662.5 $[M+Na]^+$. Anal. Calcd for $C_{31}H_{53}NO_7SSi_2$: C, 58.18; H, 8.35; N, 2.19. Found: C, 58.02; H, 8.38; N, 2.09.

3.19. 1-*O*-Benzyl-2-*N*-*tert*-butoxycarbonyl-4,6-di-*O*-*tert*-butyldimethylsilyl-2-*N*,3-*O*-thiocarbonyl-α-L-sorbofuranosylamine (19)

Yellow oil (0.42 g, 95%); $[\alpha]_D^{20}$ −36° (*c* 2, MeOH); ^{1}H NMR: δ 7.39–7.23 (m, 5 H, Ph–H), 4.68 (s, 1 H, H-3), 4.59 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.46 (d, 1 H, CH_2Ph), 4.37 (d, 1 H, $J_{4,5}$ 2.5 Hz, H-4), 4.19 (d, 1 H, $J_{1a,1b}$ 10.0 Hz, H-1a), 4.00 (td, 1 H, $J_{5,6}$ 6.3 Hz, H-5), 3.76 (d, 2 H, H-6), 3.51 (d, 1 H, H-1b), 1.52 (s, 9 H, CH_3), 0.87 (s, 9 H, CH_3), 0.83 (s, 9 H, CH_3), 0.08, 0.06, 0.04 and 0.03 (4s, 12 H, CH_3Si); ^{13}C NMR: δ 184.4 (CS), 149.1 (CO), 137.2 (C), 128.7 (CH), 128.2 (CH), 128.0 (CH), 101.2 (C-2), 89.0 (C-3), 85.2 (CMe_3), 82.8 (C-5), 74.3 (C-4), 73.6 (CH_2), 68.9 (C-1), 59.8 (C-6), 28.0 (CH_3), 26.0 (CH_3), 25.7 (CH_3), 18.4 (CMe_3), 18.0 (CMe_3), −4.8, −5.2, −5.3 (CH_3Si); ISMS (+): *m*/*z* 640.5 $[M+H]^+$. Anal. Calcd for $C_{31}H_{53}NO_7SSi_2$: C, 58.18; H, 8.35; N, 2.19. Found: C, 58.04; H, 8.46; N, 2.14.

3.20. General protocol for the preparation of the carbonyl derivatives 20 and 21

The N-Boc protected OZT (1 equiv) was dissolved in CH_2Cl_2 (1.2 M) and cooled to 0 °C; *m*-chloroperbenzoic acid (70–75%) (3 equiv) and $NaHCO_3$ (3.1 equiv) were added and the suspension was stirred for 3 h at 0 °C. After dilution with water and DCM extraction (2 ×), the collected organic phases were washed with $NaHCO_3$, water and brine, then dried over $MgSO_4$. After solvent evaporation, the crude mixture obtained was purified by chromatography (eluent A).

3.21. 1-*O*-Benzyl-2-*N*-*tert*-butoxycarbonyl-4,6-di-*O*-*tert*-butyldimethylsilyl-2-*N*,3-*O*-carbonyl-β-D-fructofuranosylamine (20)

Oil (0.27 g, 70%); $[\alpha]_D^{20}$ −28° (*c* 1.7, MeOH); ^{1}H NMR: δ 7.38–7.25 (m, 5 H, Ph–H), 4.59 (d, 1 H, $J_{3,4}$ 1.6 Hz, H-3), 4.58 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.52 (d, 1 H, CH_2Ph), 4.44 (dd, 1 H, $J_{4,5}$ 2.8 Hz, H-4), 4.20 (d, 1 H, $J_{1a,1b}$ 9.7 Hz, H-1a), 4.06–3.98 (m, 1 H, H-5), 3.64 (dd, 1 H, $J_{6a,6b}$ 10.8, $J_{5,6a}$ 4.4 Hz, H-6a), 3.60 (d, 1 H, H-1b),

3.52 (dd, 1 H, $J_{5,6b}$ 7.2 Hz, H-6b), 1.50 (s, 9 H, CH_3), 0.87 (s, 9 H, CH_3), 0.86 (s, 9 H, CH_3), 0.10, 0.08 and 0.04 (3s, 12 H, CH_3Si); ^{13}C NMR: δ 151.1 (CO), 148.6 (CO), 137.4 (C), 128.6 (CH), 128.1 (CH), 127.8 (CH), 97.6 (C-2), 88.2 (C-5), 85.9 (C-3), 84.3 (CMe_3), 76.4 (C-4), 73.5 (CH_2), 69.3 (C-1), 62.1 (C-6), 28.1 (CH_3), 26.0 (CH_3), 25.8 (CH_3), 18.0 (CMe_3), −4.8, −4.9, −5.2, −5.3 (CH_3Si); ISMS (+): m/z 646 $[M+Na]^+$, 624 $[M+H]^+$. Anal. Calcd for $C_{31}H_{53}NO_8Si_2$: C, 59.68; H, 8.56; N, 2.24. Found: C, 59.33; H, 8.58; N, 2.23.

3.22. 1-*O*-Benzyl-2-*N*-*tert*-butoxycarbonyl-4,6-di-*O*-*tert*-butyldimethylsilyl-2-*N*,3-*O*-carbonyl-α-L-sorbofuranosylamine (21)

Oil (0.21 g, 90%); $[\alpha]_D^{20}$ −36° (*c* 2, MeOH); ^1H NMR: δ 7.40–7.25 (m, 5 H, Ph–H), 4.59 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.51 (s, 1 H, H-3), 4.48 (d, 1 H, CH_2Ph), 4.28 (d, 1 H, $J_{4,5}$ 2.5 Hz, H-4), 4.25 (d, 1 H, $J_{1a,1b}$ 9.7 Hz, H-1a), 4.2 (td, 1 H, $J_{5,6}$ 6.0 Hz, H-5), 3.78 (d, 2 H, H-6), 3.47 (d, 1 H, H-1b), 1.52 (s, 9 H, CH_3), 0.87 (s, 9 H, CH_3), 0.85 (s, 9 H, CH_3), 0.09, 0.08, 0.05 and 0.04 (4s, 12 H, CH_3Si); ^{13}C NMR: δ 151.7 (CO), 148.7 (CO), 137.3 (C), 128.6 (CH), 128.1 (CH), 127.9 (CH), 97.3 (C-2), 84.2 (CMe_3), 84.1 (C-5), 82.3 (C-3), 76.3 (C-4), 73.5 (CH_2), 69.0 (C-1), 59.9 (C-6), 28.0 (CH_3), 26.0 (CH_3), 25.7 (CH_3), 18.4 (CMe_3), 18.4 (CMe_3), −4.8, −5.1, −5.2, −5.3 (CH_3Si); ISMS (+): m/z 646.5 $[M+Na]^+$. Anal. Calcd for $C_{31}H_{53}NO_8Si_2$: C, 59.68; H, 8.56; N, 2.24. Found: C, 59.31; H, 8.52; N, 2.22.

3.23. General protocol for the preparation OZO 22 and 23

The N-Boc OZO **20** and **21** (0.47 g, 0.75 mmol) was suspended in water (0.3 mL), then TFA (2.7 mL) was added. The reaction was stirred at rt until completion; after co-evaporation with toluene, the crude mixture was purified by column chromatography (eluent C).

3.24. 1-*O*-Benzyl-2-*N*,3-*O*-carbonyl-β-D-fructofuranosylamine (22)

Oil (0.145 g, 65%); $[\alpha]_D^{20}$ −17° (*c* 1, MeOH); ^1H NMR (Me_2SO): δ 8.77 (s, 1 H, NH), 7.35–7.30 (m, 5 H), 5.61 (d, 1 H, $J_{4,OH}$ 4.2 Hz, OH), 4.90 (t, 1 H, $J_{5,OH}$ 5.5 Hz, OH), 4.56 (s, 3 H, H-3, CH_2–Ph), 4.12 (s broad, 1 H, H-4), 3.86–3.80 (m, H-5), 3.60 (d, 1 H, $J_{1a,1b}$ 10.2 Hz, H-1a), 3.52 (d, 1 H, H-1b), 3.40–3.33 (m, 2 H, H-6); ^{13}C NMR (CD_3OD): δ 156.4 (CO), 137.9 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 95.7 (C-2), 86.6 (C-3), 86.1 (C-5), 75.4 (C-4), 72.5 (CH_2), 70.1 (C-1), 61.2 (C-6); ISMS (+): m/z 318 $[M+Na]^+$, 296 $[M+H]^+$. Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.95; H, 5.80; N, 4.74. Found: C, 56.51; H, 5.84; N, 4.71.

3.25. 1-*O*-Benzyl-2-*N*,3-*O*-carbonyl-α-L-sorbofuranosylamine (23)

Oil (0.075 g, 50%): $[\alpha]_D^{20}$ −16.5° (*c* 1, MeOH); ^1H NMR (CD_3OD): δ 7.42–7.24 (m, 5 H, Ph–H), 4.69 (s, 1 H, H-3), 4.61 (s, 2 H, CH_2–Ph), 4.23 (d, 1 H, $J_{4,5}$ 2.8 Hz, H-4), 4.05 (ddd, 1 H, $J_{5,6a}$ 4.7, $J_{5,6b}$ 6.6 Hz, H-5), 3.85 (dd, 1 H, $J_{6a,6b}$ 11.6 Hz, H-6a), 3.76 (dd, 1 H, H-6b), 3.74 (d, 1 H, $J_{1a,1b}$ 10.0 Hz, H-1a), 3.62 (d, 1 H, H-1b); ^{13}C NMR (CD_3OD): δ 159.9 (CO), 139.0 (C), 129.4 (CH), 128.9 (CH), 128.8 (CH), 97.2 (C-2), 87.8 (C-3), 82.0 (C-5), 75.0 (C-4), 74.6 (CH_2), 71.2 (C-1), 60.6 (C-6); ISMS (+): m/z 318 $[M+Na]^+$, 296 $[M+H]^+$. Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.95; H, 5.80; N, 4.74. Found: C, 56.55; H, 5.85; N, 4.69.

3.26. General method for the preparation of 24 and 25

A suspension of Pd/C 10% (0.3 g) in a MeOH (2 mL) solution of the 1-*O*-benzyl-OZO (0.43 g, 1.46 mmol) was stirred under H_2 overnight. After filtration over celite and chromatography (eluent D) the fully deprotected OZO was isolated.

3.27. 2-*N*,3-*O*-Carbonyl-β-D-fructofuranosylamine (24)[18]

Colorless oil (0.291 g, 100%); $[\alpha]_D^{20}$ −21° (*c* 1, MeOH); Lit.[18]: $[\alpha]_D^{20}$ −26 (*c* 0.9, EtOH).

3.28. 2-*N*,3-*O*-Carbonyl-α-L-sorbofuranosylamine (25)

Colorless oil (0.293 g, 100%): $[\alpha]_D^{20}$ −8° (*c* 1, MeOH); ^1H NMR (CD_3OD): δ 4.69 (s, 1 H, H-3), 4.24 (d, 1 H, $J_{4,5}$ 2.8 Hz, H-4), 4.04 (ddd, 1 H, $J_{5,6a}$ 6.6, $J_{5,6b}$ 4.7 Hz, H-5), 3.86 (dd, 1 H, $J_{6a,6b}$ 11.6 Hz, H-6a), 3.75 (dd, 1 H, H-6b), 3.74 (d, 1 H, $J_{1a,1b}$ 11.6 Hz, H-1a), 3.49 (d, 1 H, H-1b); ^{13}C NMR (CD_3OD): δ 160.1 (CO), 98.3 (C-2), 87.5 (C-3), 82.1 (C-5), 75.1 (C-4), 63.4 (C-1), 60.6 (C-6); ISMS (+): m/z 228 $[M+Na]^+$, 206 $[M+H]^+$. Anal. Calcd for $C_7H_{11}NO_6$: C, 40.98; H, 5.40; N, 6.83. Found: C, 41.27; H, 5.57; N, 6.77.

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