EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201300720

N-Thiocarbonyl Iminosugars: Synthesis and Evaluation of Castanospermine Analogues Bearing Oxazole-2(3*H*)-thione Moieties

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Keywords: Drug discovery / Carbohydrates / Iminosugars / Inhibitors / Nucleoside mimics

A straightforward and efficient synthetic route to a new class of glycosidase inhibitors containing an oxazole-2(3*H*)-thione moiety has been devised. The approach involves the formation of α-hydroxy ketones, which, after condensation with thiocyanic acid, leads to the formation of the heterocycle. By exploiting the ability of the nitrogen atom of oxazoline-2-thione precursors to act as nucleophiles in intramolecular addition, castanospermine analogues could be readily prepared in good overall yields. Glycosidase inhibitory activity compared to oxazolidinethione analogues showed a strong influence of the double bond, for example with pseudoiminosugar **19**, by suppressing α-glucosidase inhibition and introducing, to a moderate level, β-glucosidase inhibitory activity. Reactivities showed the propensity of oxazole-2(3*H*)-thiones – especially when fused on carbohydrate frames – to convert into 1,3-oxazolidine-2-thione aminals through nucleophilic addition to the double bond, leading to unexpected tricyclic structure **21**.

Introduction

Over the years, the chemistry and biomedical potential of iminosugars and their analogues have received a great deal of attention from the scientific community.[1] These mimetics of native sugars, in which the ring oxygen is replaced by a nitrogen atom, frequently exhibit powerful inhibitory activity towards carbohydrate-processing enzymes, including glycosidases and glycosyltransferases. Because these enzymes are involved in a plethora of key biochemical processes, compounds that allow their actions to be controlled have great potential for the treatment of a variety of diseases including viral infections,[2] bacterial infections,[3] lysosomal storage disorders,[4] cancer,[5] and diabetes.[6] However, most iminosugars are not selective and inhibit enzymes acting on anomeric substrates and some isoenzymes. Selectivity is, of course, a key issue and this behaviour has hampered their clinical application.[7] As an example (Figure 1), the piperidine-type iminosugars nojirimycin **A** and its 1-deoxy analogue **B**, which have the same hydroxylation pattern as D-glucose, are potent inhibitors of α- and β-glucosidases.[8] The related bicyclic indolizidine-type iminosugar (+)-castanospermine **C** displays higher enzyme specificity when compared with related compounds **A** or **B**, and this has been ascribed to the conformational restriction imposed by the rigidity of the system, particularly at the bond equivalent to C(5)–C(6) in hexopyranosides. Nevertheless, the anomeric specificity remains poor, which is not surprising when considering the absence of a pseudoanomeric substituent with a precise configuration at the glycosidic site.

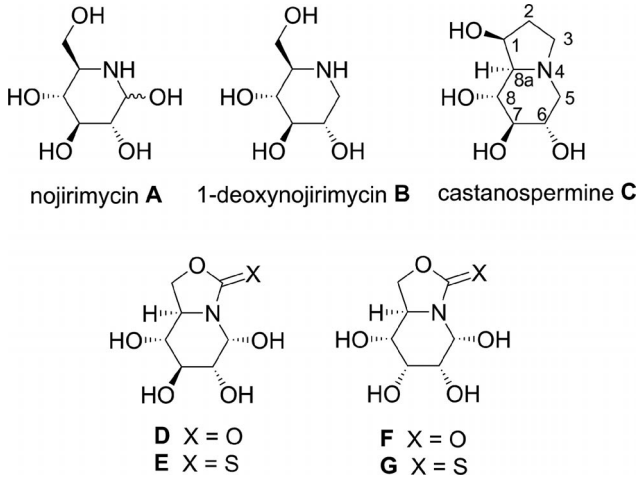

Figure 1. Structure of representative iminosugars.

In principle, installation of an oxygen substituent with a clearly defined orientation at the pseudoanomeric position in glycomimetic structures should increase the anomeric selectivity towards glycosidases by matching the stereocomplementarity of the scissile aglyconic oxygen atom in

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300720.

the natural substrate with the crucial bilateral carboxylic groups in the active site of the enzyme.[9–11] The instability of the hemiaminal functional group prevents implementation of this strategy in classical iminosugars. Replacing the sp^3 nitrogen atom with a pseudoamide-type nitrogen (with substantial sp^2 character) has been shown to dramatically enhance the stability at N–C–O segments by virtue of the generalized anomeric effect, simultaneously promoting the axial orientation of pseudoanomeric groups even in the case of reducing hemiaminal-type derivatives.[12] For instance, the bicyclic carbamate and thiocarbamate nojirimycin derivatives **D** and **E** were found exclusively in the α-configuration in water solution.[13] Interestingly, they behaved as very selective inhibitors of α-glucosidases. Structure-activity studies indicated that the endocyclic oxygen of the thiocarbamate ring was critical for inhibitory activity.[14] Modifications at the hydroxyl groups equivalent to OH-2 and OH-4 in D-glucopyranose also abolished enzyme binding.[14] The α-glucosidase inhibition activity was significantly decreased after modification at OH-3, e.g., epimerization to the D-*allo*-configured bicyclic (thio)carbamates **F** and **G**, but a higher enzyme selectivity was also observed. Further results have shown that modifications at the sp^2-iminosugar framework[15] and the incorporation of substituents at selected positions[16] offers unprecedented opportunities to control the affinity and selectivity towards glycosidases, leading to the identification of compounds with great potential for anticancer[17] and pharmacological chaperone therapies.[18]

Structural studies on sp^2-iminosugar:glycosidase complexes have shown that the piperidine ring of the bicyclic core is significantly distorted from its initial chair conformation after binding at the active site.[19] Flexibility at this region seems to be an important aspect.[20] We conceived that the incorporation of a carbon–carbon double bond at the five-membered thiocarbamate ring would alter the ground state conformation of the glycomimetic, which should translate into differences on the glycosidase inhibition profile. To test this hypothesis we have now synthesised oxazoline-2-thione-piperidine bicyclic glycomimetics with general structure **I** (Figure 2). The synthetic strategy for the preparation of compounds modified at the position analogous to C-3 in monosaccharides corresponding to C-7 in the indolizidine (trivial name for octahydroindolizine) notation, and the inhibitory activity towards a panel of commercial glycosidases in comparison with oxazolidine-2-thione partners are reported.

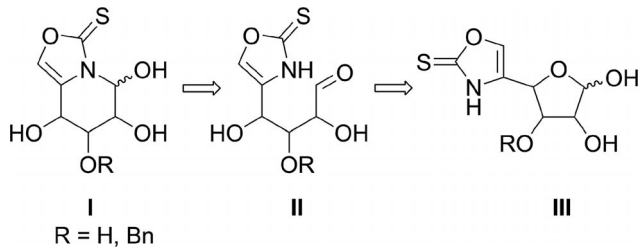


Figure 2. Retrosynthetic analysis for the target OXT-piperidine bicyclic glycomimetics.

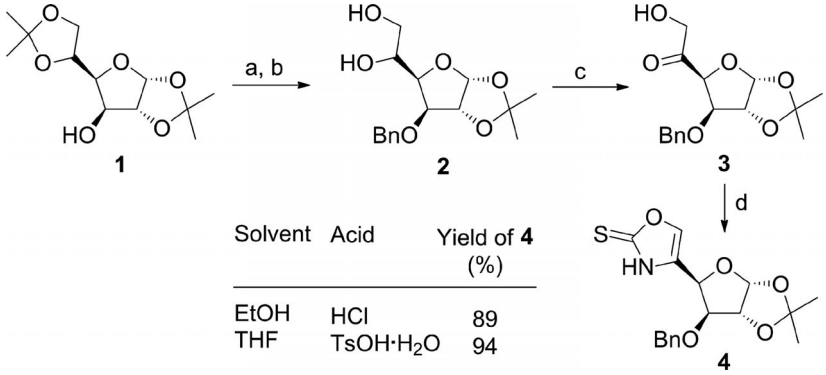
Results and Discussion

Synthesis of OXT Castanospermine Analogues

Taking advantage of our experience in the synthesis and behaviour of the oxazole-2(3*H*)-thione (OXT) motif,[21] we have performed the synthesis of a new class of castanospermine analogues in which the five-membered ring is replaced by an OXT. A retrosynthetic analysis based on previous work by Ortiz Mellet[13] presupposes that the bicyclic framework of iminosugars of type **I** can be built up through intramolecular nucleophilic addition of the nitrogen atom of five-membered ring (thio)carbamates with pseudo-*C*-nucleoside structure **III**, to the masked carbonyl in aldose precursors (Figure 2).

The initial synthetic objective of this work was to develop the simplest preparation of appropriate structures of type **III**, which, after hydrolysis, would deliver OXT-piperidine bicyclic derivatives **I**. The latter is closely related to castanospermine, with a hydroxylation pattern of the six-membered ring similar to that of D-glucose.

Starting from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (DAG, **1**), and following standard procedures,[22,23] benzylation of the 3-hydroxyl group and regioselective 5,6-*O*-isopropylidene cleavage in



Scheme 1. *Reagents and conditions:* (a) BnBr, NaH, DMF, room temp., 8 h, quantitative; (b) AcOH/H_2O (7:3), room temp., 8 h, 83%; (c) Bu_2SnO, NBS, $CHCl_3$, toluene, 85%; (d) KSCN, acid, solvent, reflux, 24 h (89–94%).

acidic medium led to the formation of diol **2** in 83% overall yield. Subsequent regioselective oxidation of the 5-hydroxyl group was performed according to Grindley,[24] by using *N*-bromosuccinimide (NBS) to efficiently oxidize a dibutylstannylene acetal, providing the 5-keto sugar **3** in 85% yield with a very high kinetic rate, as evidenced by the rapid decolouration of the reaction medium. Finally, our standard conditions (KSCN, EtOH, HCl) for OXT formation[21] were applied to reach the target compound **4** in 89% yield. Performing the reaction with $TsOH·H_2O$ in an aprotic solvent increased the yield of pseudo-*C*-nucleoside **4** to 94% (Scheme 1), with 63% overall yield from DAG **1**.

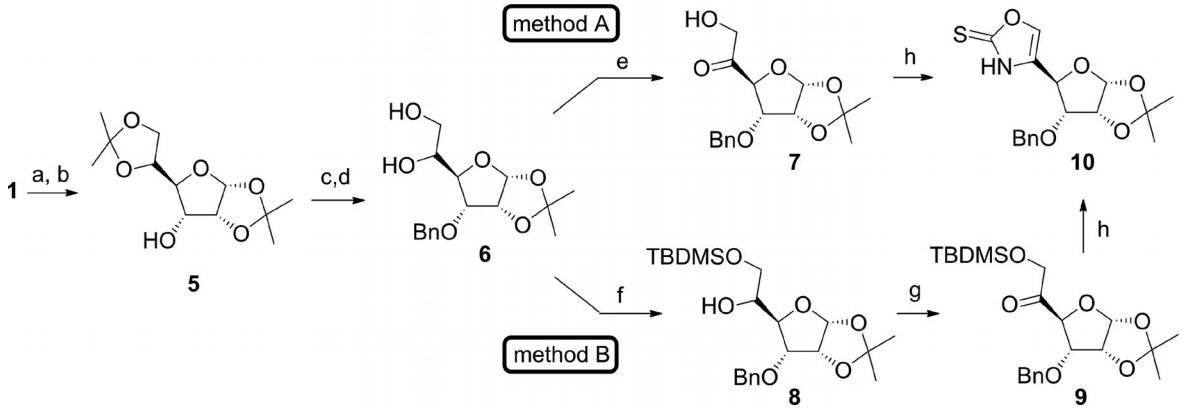
To gain insight into the selectivity of these indolizidine analogues against glycosidases, the preparation of the C-3 epimer of **4**, with D-*ribo* configuration, was then envisaged. To this end, DAG (**1**) was first subjected to a standard epimerization sequence involving pyridinium dichromate (PDC) mediated oxidation[25–27] and stereoselective $NaBH_4$ mediated reduction,[28] providing 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5**) in good yield (Scheme 2). After benzylation of the 3-OH,[29] the corresponding diacetonide was selectively hydrolysed[26] to afford diol **6** in 75% overall yield. Regioselective oxidation of the 5-hydroxyl group was then carried out by using the Bu_2SnO/NBS system[24] to provide 5-keto sugar **7** in 60% yield (Method A). The low yields obtained for this D-*ribo* keto sugar in comparison to those obtained for the D-*xylo* configured derivative **3** may be due to partial dimerisation of the α-hydroxy ketone, which depends on the configuration at C-3, as suggested in the literature.[24] Hence, dimerisation occurs to a larger extent for **7** than for **3**, in which the orientation of the C-3 substituent exerts a higher steric impedance against the formation of dimers. To prevent dimerisation, an alternative synthesis of **7** was planned following a two-step strategy (Method B). The primary hydroxyl group of **6** was first regioselectively O-silylated,[30] affording derivative **8**, which was subsequently oxidized to furnish 5-keto sugar **9** in 97% overall yield from **6**. When submitted to thiocyanic acid condensation, ketone **7**, directly, and ketone **9**, after concomitant desilylation, led to the formation of OXT **10** in an excellent 92% yield (Scheme 2).

The overall yields (41–67%) for the multi-step processes leading to the target D-*ribo* configured pseudo-*C*-nucleoside **10** were satisfactory and the synthesis proved efficient also for the D-*xylo* configured derivative. Although the second process (Method B) is longer and more costly, this allowed ketone formation in higher yield and good reproducibility – parameters to be taken into consideration when scaling up the reaction.

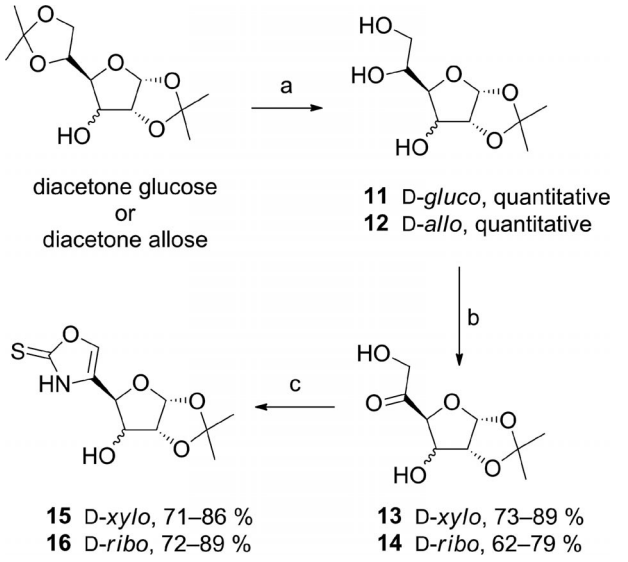
To generate OXTs as a feeler of the furanose ring, able to furnish oxaindolizine-type derivatives structurally-related to castanospermine, the synthesis of D-*xylo*- and D-*ribo*-type derivatives devoid of ether protection of the 3-OH was required. These D-*ribo* and D-*xylo* precursors were prepared by starting from DAG (**1**) or its D-*allo* epimer **5**. Selective hydrolysis of the 5,6-*O*-isopropylidene was performed with 70% aqueous AcOH[31,32] to deliver triols **11** and **12** in quantitative yield. Subsequent regioselective oxidation of the 5-OH group required optimisation of the reaction conditions. By making use of the Bu_2SnO/NBS system, α-hydroxy ketones **13** and **14** were isolated in 73 and 62% yield, respectively. Replacing NBS by Br_2 as oxidant[33,34] resulted in a yield increase to 89 and 79%, respectively. It could be observed, once again, that the oxidative conversion of a D-*gluco* species **11** is more efficient than that of its D-*allo* epimer **12**, due to easier dimer formation in the second case.

However, in our hands, and contrary to the literature,[35] bromine proved more effective than NBS for the oxidation of carbohydrate-based dialkylstannylene acetals. The α-hydroxy keto sugars **13** and **14** were then condensed with thiocyanic acid under standard conditions (EtOH, HCl, KSCN),[21] affording oxazole-2(3*H*)-thiones **15** and **16** in good yield (Scheme 3). Performing the reaction with $TsOH·H_2O$ in a 1:1 tetrahydrofuran (THF)/*N*,*N*-dimethylformamide (DMF) solution allowed the yields to be increased to 86 and 89%, respectively, thus raising the overall yield for the preparation of **15** and **16** to 77 and 70%, respectively.

Pseudo-*C*-nucleosides **4**, **10**, **15** and **16** can be prepared in reproducibly high overall yields. Curiously, the conversion of **13**–**14** into OXTs **15**–**16** was highly regioselective and no traces of isomeric six-membered ring thiocarbamate



Scheme 2. *Reagents and conditions:* (a) PDC/Ac_2O, CH_2Cl_2, quantitative; (b) $NaBH_4$, EtOH/H_2O (56:44), room temp., 3 h, 84%; (c) BnBr, NaH, DMF, room temp., 8 h, quantitative; (d) AcOH/H_2O (7:3), room temp., 8 h, 89%; (e) Bu_2SnO, NBS, $CHCl_3$, toluene, 60%; (f) TBDMSCl, imidazole, DMF, room temp., 5 h, 97%; (g) PDC/Ac_2O, CH_2Cl_2, quantitative; (h) KSCN, $TsOH·H_2O$, THF, reflux, 92%.



Scheme 3. *Reagents and conditions:* (a) AcOH/ H_2O (7:3), room temp., 8 h; (b) Bu_2SnO, NBS (or Br_2); (c) KSCN, solvent, acid.

(which would result from competitive participation of the 3-OH in the condensation) could be detected. The structure of OXTs was first confirmed by ^{13}C and ^{1}H NMR spectroscopy. The characteristic chemical shift for a C=S bond in OXT structures was detected at δ = 179.0 ppm for **4** and **10**, δ = 180.9 ppm for **15** and δ = 181.9 ppm for **16**. The H-5 resonance appeared at ca δ = 7.20 ppm for **4** and **10**, δ = 7.55 ppm for **15**, and δ = 7.64 ppm for **16**.

OXT **15** could be crystallised and its structure was confirmed by crystallographic analysis, showing only one stereoisomer in the unit (Figure 3).

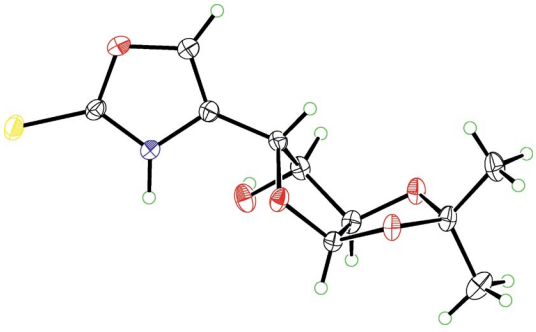
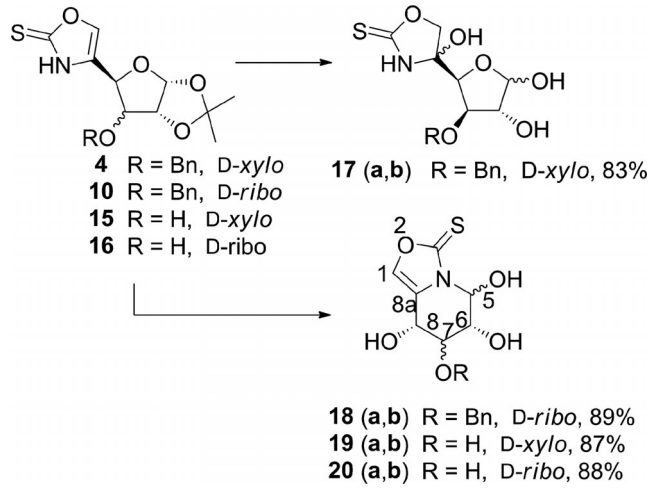


Figure 3. ORTEP diagram for compound **15** (CCDC-950949).

The feasibility of the intramolecular nucleophilic addition of the nitrogen atom in pseudo-*C*-nucleoside thiocarbamates was then investigated with the previously synthesised oxazole-2(3*H*)-thiones. Acid-catalysed hydrolysis of the anomeric acetal protecting group led to contrasting results. The 3-*O*-benzyl D-*xylo* derivative **4** was converted in 83% yield into trihydroxylated OZT **17** as a mixture of stereoisomers. Quite differently, when submitted to the same hydrolysis conditions, the 3-*O*-benzyl D-*ribo* epimer **10**, as well as the pseudo-*C*-nucleosides **15** and **16** afforded the bicyclic structures **18**, **19** and **20** in 89, 87 and 88% yield, respectively (Scheme 4).



Scheme 4. *Reagents and conditions*: TFA/H_2O (2:1), CH_2Cl_2.

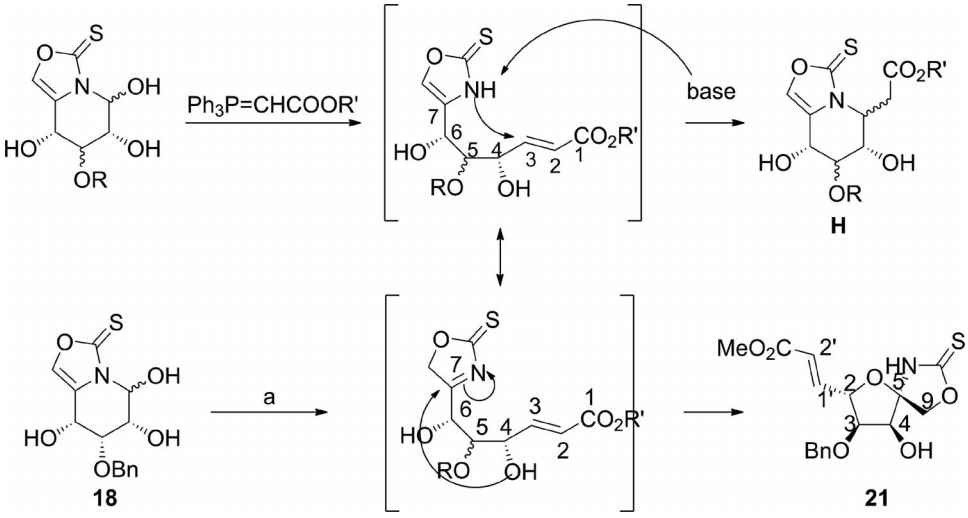
Switching to 6 M HCl as acidic medium led to very similar results. The reluctance of compound **4** to undergo intramolecular cyclisation might be ascribed to the high steric hindrance caused by the benzyl group in the 3-position. The spatial rearrangement of the latter hampers N-nucleophilic attack on the masked aldehyde, thus impeding the formation of the corresponding pseudo-iminosugar. A hydrated form of the OXT, displaying a hemiaminal-type function, is obtained instead.[36]

Compounds **18**–**20** existed in water solution as equilibrium mixtures of the corresponding *R* and *S* epimers at the hemiaminal-type pseudoanomeric stereocentre (Table 1). This situation is strikingly different from that encountered in the case of the reference (thio)carbamate glycomimetics **D**–**G**, for which a single diastereomer, matching the stereochemistry of α-glucopyranosides, was isolated. The vicinal $J_{5,6}$ proton–proton coupling constant values indicated that in both epimeric forms the pseudoanomeric hydroxyl group adopted the axial orientation. Probably, the presence of the C(8a)=C(1) double bond, which forces planarity at the C(8)–C(8a)–N segment, gives a half-chair conformation that endows the molecule with a less pronounced anomeric effect. A similar scenario has been previously reported for related bicyclic sp^2 iminosugar glycomimetics incorporating a C(7)=C(8) double bond.[15f]

Table 1. α/β Ratios and ^{13}C NMR shifts for C-5 in anomeric mixtures **18**, **19** and **20**.

	α/β ratio [%]	^{13}C NMR δ [ppm]	
		α	β
18	84:16	80.7	78.1
19	57:43	79.5	83.9
20	77:23	82.8	80.7

Overall, by exploiting the nucleophilic potency of the NH of oxazoline-2-thiones in intramolecular addition to the masked aldehyde of hexose precursors, the castanospermine analogue **19** and 7-*epi*-castanospermine analogues **18** and **20** were readily prepared.



Scheme 5. *Reagents and conditions*: (a) Ph_3P=CHCOOMe, benzoic acid, THF, reflux, 8 h, 87%.

The design and synthesis of iminosugar derivatives embodying a C–C bond linked to their pseudo-anomeric position (iminosugar *C*-glycosides[37–39]) has attracted attention since α-homonojirimycin was first synthesized by Liu[40] and thereafter isolated from a natural source.[41] It has proven to be a potent and, more significantly, selective inhibitor of α-glycosidases from the mouse gut and human intestine. Having in mind the synthesis of new α-homonojirimycin analogues, we planned the ring-opening of the iminosugar by a stabilised Wittig reagent.[42–44] Subsequent base-catalysed recyclisation of the activated olefin would afford a compound with a skeleton type **H** (Scheme 5). With this aim, compound **18** was treated with (methoxycarbonylmethylene)triphenylphosphorane in THF heated to reflux in the presence of a catalytic amount of benzoic acid, to increase the *E*-selectivity.[45] Compound **21** was formed and could be isolated in 87% yield.

The structure of **21**, and particularly the configuration of the newly formed stereocentres, was ascertained by NMR analysis using bidimensional NOESY, in which a strong NOE was observed between NH and H-3 and H-4. The formation of **21** from the transient open-chain Wittig intermediate results from a competition between two cyclisation processes involving electrophilic sites C-3 and C-7. It appears that the Michael induced ring-closure based on the NH is disfavoured, when compared to OH-4 attack on the electrophilic C=N bond under basic conditions (Scheme 5).

This interesting result brings again to question the pseudo-aromaticity of an oxazole-2(3*H*)-thione ring, which was discussed in our previous papers.[21,36] The propensity of oxazole-2(3*H*)-thiones – especially when fused on carbohydrate frames – to convert into OZT aminals through nucleophilic addition to the double bond is exemplified above by the formation of compound **17**.

Glycosidase Inhibitory Activity Evaluation

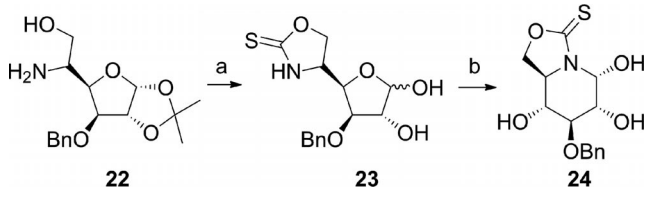
The new glycomimetics **18**–**20** were screened as glycosidase inhibitors against β-galactosidase (from bovine liver),

Table 2. Comparison of inhibitory activities (K_i, μM) for compounds **E**, **18**–**20** and **24**.[a]

Enzyme/Compounds	**E**	**24**	**18**	**19**	**20**
α-Glucosidase (yeast)	40	*ni*	688	*ni*	319
Isomaltase (yeast)	30	*ni*	*ni*	75	52
Trehalase (pig kidney)	*ni*	*ni*	505	87	416
β-Glucosidase (bovine liver)	*ni*	*ni*	*ni*	274	*ni*

[a] *ni* means no inhibitory activity was observed at [I] 2 mM against β-glucosidase (almonds), α-galactosidase (green coffee), β-galactosidase (*E. coli*), α-mannosidase (Jack beans), β-mannosidase (*Helix pomatia*) and amyloglucosidase (*Aspergillus niger*).

β-galactosidase (from *Escherichia coli*), β-glucosidase (from almonds), α-glucosidase (from yeast), α-galactosidase (from green coffee), isomaltase, trehalase (from pork kidney), α-mannosidase (from jack bean), β-mannosidase (from *Helix pomatia*) and amyloglucosidase (from *Aspergillus niger*) and the K_i values obtained are collected in Table 2. The corresponding K_i values for the previously reported[14] D-*gluco*-thiocarbamate **E** is included for comparative purposes. Additionally, the 7-*O*-benzyl derivative of **E** (**24**) was prepared in 70% overall yield by thiocarbonylation of 5-amino-5-deoxy-1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-glucofuranose (**22**)[46] and subsequent removal of the anomeric ketal by acid hydrolysis and it was also evaluated as a glycosidase inhibitor (Scheme 6).



22 **23** **24**

Scheme 6. *Reagents and conditions:* (a) CS_2, DCC, CH_2Cl_2, –10 °C to r.t, 2 h, 90%; (b) TFA/H_2O (9:1), 79%.

Surprisingly, introduction of the double bond in **19** significantly reduced the inhibition of yeast α-glucosidase (maltase), when compared to the reference (compound **E**). However inhibition of isomaltase was only slightly affected (Table 2), whereas trehalase, an α-glucosidase towards which the reference **E** was not active, was significantly inhibited by **19** (K_i = 87 μM). Weak inhibition of β-glucosidase was also noticed (K_i = 274 μM). The C-7 epimer **20** was a more potent and selective inhibitor of isomaltase (K_i = 52 μM); although it also exhibited some affinity towards maltase and trehalase, the corresponding inhibition constants were about one order of magnitude higher (K_i = 319 and 416 μM, respectively). This behaviour is drastically different from that observed for the oxazolidine analogue **G**, sharing D-*allo* configuration, which did not inhibit any of the assayed α-glucosidases. Benzylation of **20** at O-7 (→**18**) cancelled the isomaltase inhibition activity and affected to a much lesser extent the affinity towards maltase and trehalase (K_i = 688 and 505 μM, respectively).

Conclusions

We have developed a straightforward and efficient synthetic route to a new class of glycosidase inhibitors, containing an oxazole-2(3*H*)-thione moiety. The approach involves the formation of α-hydroxy ketones which, after condensation with thiocyanic acid, lead to the formation of pseudo-*C*-nucleoside precursors. By exploiting the ability of the nitrogen atom of oxazoline-2-thione precursors to act as a nucleophile in intramolecular addition to the masked aldehyde group of hexose precursors, castanospermine analogues **18**, **19** and **20** could be readily prepared in good overall yields, showing that the strategy used for the formation of these bicyclic structures is quite efficient. In contrast to what has been reported for **D**–**G** (for which the α-anomer was exclusively observed in solution), the ^{1}H NMR spectra recorded for the newly formed pseudo-iminosugars revealed the presence of both α and β-diastereomers at the hemiaminal centre. This result could be explained by comparison of oxazole-2(3*H*)-thione (OXT) and OZT structures. Whereas in iminosugar glycomimetics **D**–**G**, the imino nitrogen has substantial sp^2 character, the presence in **18**–**20** of the C(8a)=C(1) double bond, forces planarity at the C(8)–C(8a)–N segment, which results in a half-chair conformation that endows the molecule with a higher flexibility, thus allowing the anomeric effect to be fulfilled for both anomers. When applying stabilised Wittig conditions to hemiaminal **18**, a psicofurano-configured spiranic OZT was formed in excellent yield and, surprisingly, with total stereocontrol. This transformation is particularly interesting because an enantiomerically pure spiro-OZT is easily formed, which would not be feasible by condensing a ketose with thiocyanic acid.[47] Furthermore, compound **21** displays a rich chemical potential, notably with the Michael acceptor segment introduced.

Regarding the Wittig mechanism, the preferred internal cyclisation through 4-OH is made possible due to the low aromaticity character of the ring. This assumption was further confirmed by theoretical calculations related to the electronic density in the oxazole-2(3*H*)-thione ring (Figure 4).

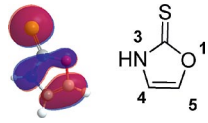


Figure 4. Electronic density in oxazole-2(3*H*)-thione ring calculated by GAMESS, using force-field type B3LYP/3-21G.

After minimisation with GAMESS, LUMO, using force-field type B3LYP/3-21G, it appeared that the C(4)–C(5) segment in oxazole-2(3*H*)-thione is relatively poor in electrons and in a more pronounced form on the C-4 carbon atom, which could explain the nucleophilic attack on C-5.

The glycosidase inhibition evaluation of the new iminosugar glycomimetics highlights the effect of structural modifications on the biological activity and supports the need for developing efficient synthetic methodologies targeting further improvement in glycosidase inhibitor properties.

Experimental Section

General: Anhydrous reactions were performed under an argon atmosphere in predried flasks, using anhydrous solvents (distilled when necessary according to ref.[49]). TLC on precoated aluminum-back plates (Merck Kieselgel 60F_{254}) were visualised by UV light (254 nm) and by charring after exposure to a 10% H_2SO_4 solution

in methanol or to a 5% solution of phosphomolybdic acid in ethanol. Flash column chromatography was carried out using Kieselgel Si60, 40–63 μM (E. Merck). Melting points [°C] were obtained with a Büchi 510 capillary apparatus and are uncorrected. Optical rotations were measured at 20 °C with a Perkin–Elmer 341 polarimeter with a path length of 1 dm. ^{1}H and ^{13}C NMR spectra were recorded with a 250 MHz Bruker Avance DPX250 spectrometer or a 400 MHz Bruker Avance2 spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from TMS internal standard and coupling constants are given in Hz. IR absorption frequencies (Thermo-Nicolet AVATAR 320 spectrometer) are given in cm^{-1}. Mass spectra were recorded with a Perkin–Elmer Sciex API 300 spectrometer for negative (ISN) and positive (ISP) electrospray ionisation. High-resolution mass spectra (HRMS) were recorded with a MicrOTOF-QII spectrometer in the electrospray ionisation (ESI) mode or in chemical ionisation (CI) mode.

Materials: 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**3**) was obtained in three steps from DAG (**1**), as previously reported.[24] 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranos-5-ulose (**7**) was prepared in five steps from DAG (**1**), as previously reported.[48] (5*R*,6*R*,7*R*,8*R*,8a*R*)5,6,7,8-Tetrahydroxy-3-(thio)xo-2-oxaindolizidines were prepared by following reported procedures.[14]

4-[(4*R*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-threofuranos-4-*C*-yl]-1,3-oxazoline-2-thione (4): The ulose **3** (83.3 mg, 0.27 mmol) and KSCN (39.8 mg, 0.41 mmol) were dissolved in THF (10 mL). After cooling at –5 °C, TsOH·H$_2$O (102.7 mg, 0.54 mmol) was carefully added and the mixture was heated to reflux with stirring for 24 h, then cooled by adding crushed ice. After extraction with EtOAc (3× 25 mL), the combined organic phase was washed with saturated aqueous NaHCO$_3$, water, and brine, and finally dried with MgSO$_4$. After filtration and concentration under vacuum, the residue was purified by column chromatography (PE/EtOAc, 8:2) to afford **4** (88.7 mg, 94%) as a yellow oil. $[\alpha]_D$ = –16 (c = 1.0, MeOH, 25 °C). IR (NaCl): $\tilde{\nu}_{max}$ = 3230 (NH), 2986, 2909, 1636 (C=C), 1492, 1130 (N–CS–O), 1469, 1464 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.32 and 1.50 (2× s, 6 H, *Me*$_2$C), 4.02 (d, $J_{3'-4'}$ = 3.1 Hz, 1 H, H-3′), 4.45 and 4.65 (2× d, AB system, J_{gem} = 11.7 Hz, 2 H, O*CH*$_2$Ph), 4.69 (d, $J_{1'-2'}$ = 3.3 Hz, H-2′), 5.04 (d, $J_{3'-4'}$ = 3.1 Hz, 1 H, H-4′), 5.99 (d, 1 H, H-1′), 7.20–7.27 (m, 3 H, H-5, Ph), 7.29–7.38 (m, 3 H, Ph), 11.00 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 26.0, 26.7 (*Me*$_2$C), 72.1 (C-4′), 72.4 (O*CH*$_2$Ph), 82.0 (C-2′), 82.4 (C-3′), 104.8 (C-1′), 112.4 (Me$_2$*C*), 125.9 (C-4), 128.1, 128.4, 128.7 (CH-Ph), 134.8 (C-5), 136.2 (C$_{IV}$-Ph), 179.0 (C=S) ppm. HRMS: calcd. for C$_{17}$H$_{20}$NO$_5$S [M + H]$^+$ 350.1062; found 350.1054.

3-*O*-Benzyl-6-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-allofuranose (8): To diol **6** (117.9 mg, 0.38 mmol) dissolved in anhydrous DMF (10 mL) at 0 °C were added imidazole (51.7 mg, 0.76 mmol) and TBDMSCl (85.8 mg, 0.57 mmol). The reaction was stirred for 5 h at room temperature, then treated with crushed ice. After extraction with EtOAc (3× 20 mL), the combined organic phase was washed with water and brine, and finally dried with MgSO$_4$. After filtration and concentration under vacuum, the residue was purified by column chromatography (PE/EtOAc, 7:3) to afford **8** (156.5 mg, 97%) as a white solid; m.p. 115–116 °C. $[\alpha]_D$ = +43 (c = 0.5, CHCl$_3$, 25 °C). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.06 (s, 6 H, *Me*$_2$Si), 0.89 (s, 9 H, *tBu*Si), 1.58 and 1.59 (2× s, 6 H, *Me*$_2$C), 2.53 (d, J_{5-OH} = 3.1 Hz, 1 H, OH), 3.62–3.72 (m, 2 H, H-6a, H-6b), 3.88–3.93 (m, 1 H, H-5), 3.96 (dd, J_{2-3} = 4.5 Hz, J_{3-4} = 8.7 Hz, 1 H, H-3), 4.06 (dd, J_{4-5} = 4.2 Hz, 1 H, H-4), 4.55 (t, J_{2-3} = 4.5 Hz, 1 H, H-2), 4.60 and 4.76 (2× d, AB system, J_{gem} = 11.7 Hz, 2 H, O*CH*$_2$Ph), 5.74 (d, J_{1-2} = 3.8 Hz, 1 H, H-1), 7.28–7.40 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = –4.7, –4.8 (*Me*$_2$Si), 18.5 (C$_{IV}$-*t*Bu), 26.0 (*t*Bu), 26.7, 26.9 (*Me*$_2$C), 63.9 (C-6), 72.1 (C-5), 72.3 (O*CH*$_2$Ph), 77.9 (C-2), 78.0 (C-3), 78.1 (C-4), 104.2 (C-1), 113.1 (Me$_2$*C*), 128.1, 128.2, 128.6 (CH-Ph), 137.7 (C$_{IV}$-Ph) ppm. HRMS: calcd. for C$_{22}$H$_{36}$O$_6$SiNa [M + Na]$^+$ 447.2179; found 447.2183.

3-*O*-Benzyl-6-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranos-5-ulose (9): Compound **8** (150.0 mg, 0.35 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (10 mL). PDC (79.0 mg, 0.21 mmol) and Ac$_2$O (0.13 mL, 1.38 mmol) were added and the reaction was heated to reflux and stirred for 2 h. After concentration of the mixture in vacuo, the residue was applied to a short silica gel column (EtOAc) and the filtrate was co-evaporated with toluene (3×). Compound **9** was obtained quantitatively as a yellow oil. $[\alpha]_D$ = +16 (c = 1.0, CHCl$_3$, 25 °C). IR (NaCl): $\tilde{\nu}$ = 1727 (C=O), 1461 (Ph), 1215 (Si(CH$_3$)$_2$) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.08 (s, 6 H, *Me*$_2$Si), 0.91 (s, 9 H, *t*BuSi), 1.36 and 1.60 (2× s, 6 H, *Me*$_2$C), 3.87 (dd, J_{2-3} = 4.0 Hz, J_{3-4} = 9.1 Hz, 1 H, H-3), 4.49 (s, 2 H, H-6a, H-6b), 4.54 (t, J_{2-3} = 4.5 Hz, 1 H, H-2), 4.60 (d, 1 H, H-4), 4.63 and 4.75 (2× d, AB system, J_{gem} = 11.9 Hz, 2 H, O*CH*$_2$Ph), 5.81 (d, J_{1-2} = 4.5 Hz, 1 H, H-1), 7.31–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = –4.7, –4.8 (*Me*$_2$Si), 18.6 (C$_{IV}$-*t*Bu), 25.9 (*t*Bu), 26.6, 27.0 (*Me*$_2$C), 68.0 (C-6), 72.5 (O*CH*$_2$Ph), 77.9 (C-2), 79.6 (C-3), 80.0 (C-4), 104.7 (C-1), 113.7 (Me$_2$*C*), 128.2, 128.6, 129.1 (CH-Ph), 137.1 (C$_{IV}$-Ph), 205.0 (C=O) ppm. MS (IS): m/z = 423.5 [M + H]$^+$. HRMS: calcd. for C$_{22}$H$_{35}$O$_6$Si [M + H]$^+$ 423.2203; found 423.2211.

4-[(4*R*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-erythrofuranos-4-*C*-yl]-1,3-oxazoline-2-thione (10); Method A (from 9): The ulose **9** (114.1 mg, 0.27 mmol) and KSCN (39.8 mg, 0.41 mmol) were dissolved in THF (15 mL). After cooling at –5 °C, TsOH·H$_2$O (102.7 mg, 0.54 mmol) was carefully added and the mixture was heated to reflux and stirred for 24 h, then cooled by adding crushed ice. After extraction with EtOAc (3× 25 mL), the combined organic phase was washed with saturated aqueous NaHCO$_3$, water, and brine, and finally dried with MgSO$_4$. After filtration and concentration under vacuum, the residue was purified by column chromatography (cyclohexane/EtOAc, 6:4) to afford **10** (86.7 mg, 92%) as a white solid. **Method B (from 7)**: The ulose **7** (100.0 mg, 0.32 mmol) and KSCN (46.6 mg, 0.48 mmol) were dissolved in THF (15 mL). After cooling at –5 °C, TsOH·H$_2$O (121.7 mg, 0.64 mmol) was carefully added and the mixture was heated to reflux and stirred for 24 h, then cooled by adding crushed ice. After extraction with EtOAc (3× 25 mL), the combined organic phase was washed with saturated aqueous NaHCO$_3$, water, and brine, and finally dried with MgSO$_4$. After filtration and concentration under vacuum, the residue was purified by column chromatography (cyclohexane/EtOAc, 6:4) to afford **10** (102.8 mg, 92%) as a white solid; m.p. 174–175 °C. $[\alpha]_D$ = –50 (c = 1.0, MeOH, 25 °C). IR (NaCl): $\tilde{\nu}$ = 3223 (NH), 2987, 2910, 1650 (C=C), 1497, 1112 (N–CS–O), 1465, 1454 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.37 and 1.61 (2× s, 6 H, *Me*$_2$C), 3.89 (dd, $J_{2'-3'}$ = 4.0 Hz, $J_{3'-4'}$ = 9.0 Hz, 1 H, H-3′), 4.52 and 4.75 (2× d, AB system, J_{gem} = 11.8 Hz, 2 H, O*CH*$_2$Ph), 4.68 (br. t, 1 H, H-2′), 4.87 (d, 1 H, H-4′), 5.83 (d, $J_{1'-2'}$ = 3.4 Hz, 1 H, H-1′), 7.20 (s, 1 H, H-5), 7.25–7.36 (m, 5 H, Ph), 11.78 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 26.4, 26.8 (*Me*$_2$C), 70.5 (C-4′), 72.6 (O*CH*$_2$Ph), 77.0 (C-2′), 80.7 (C-3′), 104.3 (C-1′), 113.8 (Me$_2$*C*), 128.3 (C-4), 128.3, 128.5, 128.6 (CH-Ph), 134.8 (C-5), 136.6 (C$_{IV}$-Ph), 179.1 (C=S) ppm. HRMS: calcd. for C$_{17}$H$_{20}$NO$_5$S [M + H]$^+$ 350.1062; found 350.1056.

1,2-*O*-Isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (13): Triol **11** (178.4 mg, 0.81 mmol) was dissolved in anhydrous MeOH (10 mL) and dibutyltin oxide (403.3 mg, 1.62 mmol) was added. After heating to reflux and stirring for 2 h, the solvent was evaporated and the residue was dried under vacuum for 30 min. The residue was then taken up in anhydrous CH_2Cl_2 (10 mL) and Br_2 (42 μL, 0.82 mmol) was added. The resulting solution was stirred for 20 min, then the solvent was evaporated and the residue was purified by column chromatography (PE/EtOAc, 1:1) to afford **13** (157.3 mg, 89%) as a colourless oil. $[\alpha]_D$ = –50 (*c* = 1.1, $CHCl_3$, 25 °C). IR (NaCl): $\tilde{\nu}$ = 1727 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 and 1.48 (2× s, 6 H, Me_2C), 3.83 (br. s, 1 H, OH), 4.12 (br. s, 1 H, OH), 4.46 (d, J_{6-OH} = 3.5 Hz, 2 H, H-6a, H-6b), 4.55 (d, J_{1-2} = 3.5 Hz, 1 H, H-2), 4.56 (d, J_{3-4} = 3.3 Hz, 1 H, H-3), 4.75 (d, J_{3-4} = 3.3 Hz, 1 H, H-4), 6.06 (d, 1 H, H-1) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3, 26.9 (Me_2C), 68.0 (C-6), 76.3 (C-3), 84.6 (C-2), 85.3 (C-4), 105.8 (C-1), 112.5 (Me_2C), 209.1 (C=O) ppm. HRMS: calcd. for $C_9H_{14}O_6Na$ $[M + Na]^+$ 241.0688; found 241.0686.

4-[(4*R*)-1,2-*O*-Isopropylidene-α-D-threofuranos-4-*C*-yl]-1,3-oxazoline-2-thione (15): The ulose **13** (151.0 mg, 0.69 mmol) and KSCN (100.6 mg, 1.04 mmol) were dissolved in THF/DMF (1:1, 15 mL). After cooling at –5 °C, $TsOH·H_2O$ (262.5 mg, 1.38 mmol) was carefully added and the mixture was heated to reflux and stirred for 24 h, then cooled by adding crushed ice. After extraction with EtOAc (3× 25 mL), the combined organic phase was washed with saturated aqueous $NaHCO_3$, water, and brine, and finally dried with $MgSO_4$. After filtration and concentration under vacuum, the residue was purified by column chromatography (cyclohexane/EtOAc, 1:2) to afford **15** (153.9 mg, 86%) as a yellow solid; m.p. 148–149 °C. $[\alpha]_D$ = –58 (*c* = 0.6, $CHCl_3$, 25 °C). IR (NaCl): $\tilde{\nu}$ = 3480 (OH), 3240 (NH), 2974, 2954, 1655 (C=C), 1503, 1375, 1108 (N–CS–O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 and 1.44 (2× s, 6 H, Me_2C), 3.41 (br. s, 1 H, OH), 4.32 (d, $J_{3'-4'}$ = 2.8 Hz, 1 H, H-3′), 4.63 (d, $J_{1'-2'}$ = 3.5 Hz, 1 H, H-2′), 5.12 (d, 1 H, H-4′), 5.98 (d, 1 H, H-1′), 7.56 (s, 1 H, H-5), 11.59 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [d_6]acetone): δ = 27.6, 28.0 (Me_2C), 75.1 (C-4′), 77.4 (C-3′), 86.8 (C-2′), 106.4 (C-1′), 113.3 (Me_2C), 128.4 (C-4), 136.4 (C-5), 180.9 (C=S) ppm. HRMS: calcd. for $C_{10}H_{14}NO_5S$ $[M + H]^+$ 260.0593; found 260.0600.

1,2-*O*-Isopropylidene-α-D-*ribo*-hexofuranos-5-ulose (14): Triol **12** (178.4 mg, 0.81 mmol) was dissolved in anhydrous MeOH (10 mL) and dibutyltin oxide (403.3 mg, 1.62 mmol) was added. After heating to reflux and stirring for 2 h, the solvent was evaporated and the residue was dried under vacuum for 30 min. The residue was taken up in anhydrous CH_2Cl_2 (10 mL) and Br_2 (42 μL, 0.82 mmol) was added. The resulting solution was stirred for 20 min, then the solvent was evaporated and the residue was purified by column chromatography (PE/EtOAc, 2:8) to afford **14** (139.6 mg, 79%) as a colourless oil. $[\alpha]_D$ = +63 (*c* = 1.2, $CHCl_3$, 25 °C). IR (NaCl): $\tilde{\nu}$ = 1730 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 and 1.58 (2× s, 6 H, Me_2C), 4.09–4.15 (m, 3 H, H-3, H-6a, H-6b), 4.39 (d, J_{3-4} = 9.2 Hz, 1 H, H-4), 4.50 (br. s, 2 H, OH), 4.65 (br. t, J_{2-3} = 4.1 Hz, 1 H, H-2), 5.89 (d, J_{1-2} = 3.8 Hz, 1 H, H-1) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.4, 26.5 (Me_2C), 66.1 (C-6), 73.8 (C-3), 78.8 (C-2), 81.8 (C-4), 104.2 (C-1), 113.4 (Me_2C), 207.8 (C=O) ppm. HRMS: calcd. for $C_9H_{14}O_6Na$ $[M + Na]^+$ 241.0688; found 241.0676.

4-[(4*R*)-1,2-*O*-Isopropylidene-α-D-erythrofuranos-4-*C*-yl]-1,3-oxazoline-2-thione (16): The ulose **14** (151.0 mg, 0.69 mmol) and KSCN (100.6 mg, 1.04 mmol) were dissolved in THF/DMF (1:1, 15 mL). After cooling at –5 °C, $TsOH·H_2O$ (262.5 mg, 1.38 mmol) was carefully added and the mixture was heated to reflux and stirred for 24 h, then cooled by adding crushed ice. After extraction with EtOAc (3× 25 mL), the combined organic phase was washed, with saturated aqueous $NaHCO_3$, water, and brine, and finally dried with $MgSO_4$. After filtration and concentration under vacuum, the residue was purified by column chromatography (PE/EtOAc, 4:6) to afford **16** (159.2 mg, 89%) as a white solid; m.p. 145–146 °C. $[\alpha]_D$ = –57 (*c* = 1.5, $CHCl_3$, 25 °C). IR (NaCl): $\tilde{\nu}$ = 3479 (OH), 3200 (NH), 2986, 2940, 1655 (C=C), 1474, 1374, 1140 (N–CS–O) cm^{-1}. ^1H NMR (400 MHz, [d_6]acetone): δ = 1.31 and 1.49 (2× s, 6 H, Me_2C), 4.18–4.19 (m, 1 H, H-3′), 4.45 (br. s, 1 H, OH), 4.69 (br. t, $J_{2'-3'}$ = 4.2 Hz, 1 H, H-2′), 4.73 (d, $J_{3'-4'}$ = 9.0 Hz, 1 H, H-4′), 5.82 (d, $J_{1'-2'}$ = 3.6 Hz, 1 H, H-1′), 7.63 (s, 1 H, H-5), 11.90 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [d_6]acetone): δ = 27.6, 27.9 (Me_2C), 73.6 (C-4′), 76.4 (C-3′), 80.8 (C-2′), 105.8 (C-1′), 114.3 (Me_2C), 130.2 (C-4), 136.7 (C-5), 181.9 (C=S) ppm. HRMS: calcd. for $C_{10}H_{14}NO_5S$ $[M + H]^+$ 260.0593; found 260.0586.

4-Hydroxy-4-[(4′*S*)-3-*O*-benzyl-α-D-threofuranos-4′-*C*-yl]-1,3-oxazolidine-2-thione (17): A solution of oxazole-2(3*H*)-thione **4** (101.0 mg, 0.29 mmol) in CH_2Cl_2/TFA/H_2O (2:2:1, 10 mL) was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was co-evaporated several times with water and, after concentration under vacuum, purified by column chromatography (PE/EtOAc, 7:3) to afford the stereoisomeric mixture **17** (78.8 mg, 83%; α/β: 3:7) as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 4.02 (d, $J_{3'\alpha-4'\alpha}$ = 3.2 Hz, 4′-Hα), 4.16 (br. s, 3′-Hβ), 4.35–4.37 (m, 2′-Hβ), 4.63–4.70 (m, 2′-Hα, 4′-Hβ, OCH_2-Phα, OCH_2Phβ, H-5aα, H-5aβ, H-5bα, H-5bβ), 4.99 (d, $J_{3'\alpha-4'\alpha}$ = 3.2 Hz, 3′-Hα), 5.68 (br. s, 1′-Hβ), 5.99 (d, $J_{1'\alpha-2'\alpha}$ = 3.8 Hz, 1′-Hα), 7.28–7.35 (m, Ph), 9.80 (br. s, NH) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 73.4, 73.6 (OCH_2Ph), 74.9, 75.0 (C-4′α, C-4′β), 77.4, 77.5 (C-5), 78.1, 79.8 (C-2′α, C-2′β), 83.6, 83.8 (C-3′α, C-3′β), 97.0 (C-1′α), 105.0 (C-1′β), 112.6, 112.7 (C-4), 127.5, 128.1, 128.7, 128.9, 129.0, 129.4 (CH-Ph), 135.4, 135.6 (C_{IV}-Ph), 187.6, 188.3 (C=S) ppm. HRMS: calcd. for $C_{14}H_{18}NO_6S$ $[M + H]^+$ 328.0855; found 328.0845.

(6*R*,7*R*,8*R*)-7-Benzyloxy-5,6,8-trihydroxy-2,3,5,6,7,8-hexahydro-3-thioxo-2-oxaindolizine (18): A solution of OXT **10** (101.0 mg, 0.29 mmol) in CH_2Cl_2/TFA/H_2O (2:2:1, 10 mL) was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was co-evaporated several times with water and, after concentration under vacuum, purified by column chromatography (PE/EtOAc, 1:1) to afford the anomeric mixture **18** (79.8 mg, 89%; α/β: 8:2) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.67 (br. s, OH), 3.82 (dd, $J_{6\beta-7\beta}$ = 4.0, $J_{7\beta-8\beta}$ = 1.5 Hz, 7-Hβ), 3.98 (dd, $J_{6\alpha-7\alpha}$ = 3.9, $J_{7\alpha-8\alpha}$ = 1.6 Hz, 7-Hα), 4.06 (br. s, OH), 4.18–4.23 (m, 6-Hα 6-Hβ), 4.73 and 4.80 (2× d, AB system, J_{gem} = 11.3 Hz, 2 H, OCH_2Ph), 4.84 (br. s, H-8α, H-8β), 5.47 (br. s, OH), 5.54 (br. t, $J_{5\beta-6\beta}$ = 4.3 Hz, H-5β), 5.69 (d, $J_{1\alpha-8a\alpha}$ = 3.5 Hz, H-5α), 5.99 (d, $J_{5\beta-OH}$ = 4.5 Hz, OH), 7.30–7.36 (m, Ph, H-1α, H-1β) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.6 (C-8α), 61.9 (C-8β), 68.9 (C-6β), 71.8 (C-6α), 72.9 (OCH_2Ph-α), 73.5 (OCH_2Ph-β), 74.0 (C-7α), 75.5 (C-7β), 78.1 (C-5β), 80.7 (C-5α), 128.3, 128.4, 128.6, 128.7, 128.9, 129.0, 129.6 (CH-Ph), 134.4 (C_{IV}-Ph, C-1α), 134.6 (C-1β), 136.6 (C-8aβ), 136.9 (C-8aα), 178.1, 178.2 (C=S) ppm. HRMS: calcd. for $C_{14}H_{15}NO_5SNa$ $[M + Na]^+$ 332.0569; found 332.0586.

(6*R*,7*S*,8*R*)-5,6,7,8-Tetrahydroxy-2,3,5,6,7,8-hexahydro-3-thioxo-2-oxaindolizine (19): A solution of the oxazole-2(3*H*)-thione **15** (101.0 mg, 0.39 mmol) in CH_2Cl_2/TFA/H_2O (2:2:1, 10 mL) was

stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was co-evaporated several times with water and, after concentration under vacuum, purified by column chromatography (EtOAc) to afford the anomeric mixture **19** (74.4 mg, 87%; α/β: 57:43) as a colourless oil. ^{1}H NMR (400 MHz, [d_6]acetone): δ = 3.64–3.74 (m, 6-Hα, 7-Hβ), 3.88–3.93 (m, 7-Hα, 6-Hβ), 4.28 (d, $J_{6\alpha-OH}$ = 6.8 Hz, OH), 4.43–4.47 (m, 8-Hα, OH), 4.58–4.62 (m, 8-Hβ), 4.87 (d, $J_{7\beta-OH}$ = 4.7 Hz, OH), 4.92–5.00 (m, OH), 5.41 (t, $J_{5\beta-6\beta}$ = 4.8 Hz, 5-Hβ), 5.67 (t, $J_{5\alpha-6\alpha}$ = 3.8 Hz, 5-Hα), 5.86 (d, $J_{5\beta-OH}$ = 4.8 Hz, OH), 6.04 (d, $J_{5\alpha-OH}$ = 3.8 Hz, OH), 7.39 (d, $J_{1\alpha-8a\alpha}$ = 1.8 Hz, 1-Hα), 7.43 (d, $J_{1\beta-8a\beta}$ = 1.7 Hz, 1-Hβ) ppm. ^{13}C NMR (100 MHz, [d_6]acetone): δ = 66.6 (C-8β), 67.8 (C-8α), 71.2 (C-7α), 71.8 (C-7β), 74.5, 75.3 (C-6), 79.5 (C-5α), 83.9 (C-5β), 131.7, 131.8 (C-8a), 133.6 (C-1β), 133.7 (C-1α), 179.6 (C=S) ppm. HRMS: calcd. for $C_7H_{10}NO_5S$ [M + H]$^+$ 220.0280; found 220.0271.

(6*R*, 7*R*, 8*R*)-5,6,7,8-Tetrahydroxy-2,3,5,6,7,8-hexahydro-3-thioxo-2-oxaindolizine (20): A solution of OXT **16** (101.0 mg, 0.39 mmol) in CH_2Cl_2/TFA/H_2O (2:2:1, 10 mL) was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was co-evaporated several times with water and, after concentration under vacuum, purified by column chromatography (EtOAc) to afford the anomeric mixture **20** (75.2 mg, 88%; α/β: 77:23) as a colourless oil. ^{1}H NMR (400 MHz, [d_6]acetone): δ = 2.86 (br. s, OH), 3.90–3.91 (m, 6-Hβ), 3.98–3.99 (m, 6-Hα), 4.05–4.06 (m, 7-Hα), 4.17 (br. s, 7-Hβ), 4.70–4.71 (m, 8-Hβ), 4.77 (br. s, 8-Hα), 5.50 (d, $J_{5\alpha-6\alpha}$ = 3.9 Hz, 5-Hα), 5.53 (d, $J_{5\beta-6\beta}$ = 4.9 Hz, 5-Hβ), 7.41 (s, 1-Hβ), 7.47 (s, 1-Hα) ppm. ^{13}C NMR (100 MHz, [d_6]acetone): δ = 64.9 (C-8α), 65.9 (C-8β), 68.9 (C-6β), 70.6 (C-7α), 74.3 (C-7β), 75.0 (C-6α), 80.7 (C-5β), 82.8 (C-5α), 132.9 (C-8a), 135.6 (C-1), 180.2 (C=S) ppm. HRMS: calcd. for $C_7H_{10}NO_5S$ [M + H]$^+$ 220.0280; found 220.0271.

(2*S*,3*S*,4*S*,5*S*,1′*E*)-2-(2′-Methoxycarbonyl)vinyl-3-benzyloxy-4-hydroxy-6-aza-1,8-dioxaspiro[4.4]nonane-7-thione (21): The iminosugar **18** (92.8 mg, 0.30 mmol) was dissolved in anhydrous THF (10 mL). (Methoxycarbonylmethylene)triphenylphosphorane (0.42 g,1.26 mmol) and benzoic acid (2.6 mg, 0.021 mmol) were added and the reaction was heated to reflux and stirred for 8 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (PE/EtOAc, 6:4) to afford **21** (95.4 mg, 87%) as a yellow oil. $[\alpha]_D$ = +33 (c = 0.6, $CHCl_3$, 25 °C). IR (NaCl): $\tilde{\nu}$ = 3480 (OH), 3250 (NH), 3032, 2922, 2852, 1715 (C=O), 1648 (C=C), 1484, 1170 (N–CS–O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.04 (d, J_{4-OH} = 4.8 Hz, 1 H, OH), 3.75 (s, 3 H, OMe), 3.95 (t, J_{3-4} = J_{2-3} = 4.6 Hz, 1 H, 3-H), 4.13 (br. t, J_{3-4} = 4.6 Hz, 1 H, 4-H), 4.54 (d, J_{gem} = 11.0 Hz, 1 H, 9-Hb), 4.58 (dt, $J_{2-2'}$ = 1.7, J_{2-3} = $J_{2-1'}$ = 4.6 Hz, 1 H, 2-H), 4.63 and 4.69 (2× d, AB system, J_{gem} = 11.5 Hz, 2 H, OCH_2Ph), 4.95 (d, 1 H, H-9a), 6.10 (dd, $J_{1'-2'}$ = 15.6 Hz, 1 H, H-2′), 6.84 (dd, 1 H, H-1′), 7.31–7.39 (m, 5 H, Ph), 8.58 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.1 (OMe), 72.8 (C-4), 73.6 (OCH_2Ph), 76.9 (C-9), 79.7 (C-2), 81.1 (C-3), 98.9 (C-5), 122.4 (C-2′), 128.3, 128.9, 129.1 (CH-Ph), 136.3 (C_{IV}-Ph), 143.8 (C-1′), 166.6 (C=O), 189.9 (C=S) ppm. HRMS: calcd. for $C_{17}H_{20}NO_6S$ [M + H]$^+$ 366.1011; found 366.1000.

Preparation of (5*R*,6*R*,7*S*,8*R*,8a*R*)-7-Benzyloxy-5,6,8-trihydroxy-1,2,3,5,6,7,8, 8a-octahydro-3-thioxo-2-oxaindolizine (24)

4-[(4′*R*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-threofuranos-4′-C-yl]-1,3-oxazolidine-2-thione (23): CS_2 (0.80 mL, 13.2 mmol, 10.0 equiv.) and DCC (272 mg, 1.32 mmol, 1.0 equiv.) were added to a stirred solution of 5-amino-5-deoxy-1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-glucofuranose (**22**;[46] 408 mg, 1.32 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (12 mL) at –10 °C. The reaction mixture was allowed to reach room temperature and stirred for 2 h (TLC monitoring). After solvent removal under reduced pressure, the residue was purified by column chromatography (1:5→1:2.5 EtOAc/PE) to afford the OZT **23** (417 mg, 90%) as a white foam. $[\alpha]_D$ = –88 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 and 1.52 (2× s, 6 H, Me_2C), 4.03 (d, $J_{3,4}$ = 3.5 Hz, 1 H, H-3′), 4.23–4.30 (m, 2 H, H-4′, H-4), 4.49 and 4.76 (2× d, AB system, J_{gem} = 12.0 Hz, 2 H, OCH_2Ph), 4.69 (d, 1 H, H-2′), 4.69–4.72 (m, 2 H, H-5), 5.95 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1′), 7.30–7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 26.3, 26.8 (Me_2C), 55.2 (C-4), 71.7 (OCH_2Ph), 72.7 (C-5), 80.1 (C-4′), 81.3 (C-3′), 81.7 (C-2′), 105.3 (C-1′), 112.3 (Me_2C), 128.1, 128.4, 128.7 (CH-Ph), 137.0 (C_{IV}-Ph), 189.6 (C=S) ppm. MS (ESI): m/z = 374.0 [M + Na]$^+$. $C_{17}H_{21}NO_5S$ (351.42): calcd. C 58.10, H 6.02, N 3.99, S 9.12; found C 58.15, H 5.93, N 3.81, S 8.94.

Conversion of 23 into the Hemi-Aminal 24: A solution of the OZT **23** (200 mg, 0.57 mmol) in 90% TFA/H_2O (6 mL) was stirred at room temperature for 1 h. After solvent removal under reduced pressure, the residue was coevaporated several times with water, treated with NaOH 0.1 N until pH 8, then concentrated under reduced pressure. The resulting residue was purified by column chromatography (1:1→2:1 EtOAc/PE) to give **24** (140 mg, 79%) as a white foam. $[\alpha]_D$ = +20 (c = 1.0, MeOH). ^{1}H NMR (500 MHz, MeOD): δ = 3.45 (t, $J_{8,8a}$ = 9.5 Hz, 1 H, 8-H), 3.55 (dd, 1 H, 6-H), 3.72 (t, $J_{6,7}$ = $J_{7,8}$ = 9.5 Hz, 1 H, 7-H), 4.07–4.15 (m, 1 H, 8-Ha), 4.46 (dd, $J_{1b,8a}$ = 6.0 Hz, 1 H, 1-Hb), 4.70 (t, $J_{1a,1b}$ = $J_{1a,8a}$ = 9.0 Hz, 1 H, 1-Ha), 4.88 and 4.93 (2× d, AB system, J_{gem} = 11.0 Hz, 2 H, OCH_2Ph), 5.81 (d, $J_{5,6}$ = 3.5 Hz, 1 H, H-5), 7.25–7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (125.7 MHz, MeOD): δ = 57.0 (C-8a), 71.1 (C-1), 71.3 (C-6), 73.5 (C-8), 75.1 (OCH_2Ph), 78.8 (C-5), 81.4 (C-7), 127.2–127.8 (CH-Ph), 138.9 (C_{IV}-Ph), 186.6 (CS) ppm. MS (ESI): m/z = 334.0 [M + Na]$^+$. $C_{14}H_{17}NO_5S$ (311.35): calcd. C 54.01, H 5.50, N 4.50, S 10.30; found C 53.87, H 5.29, N 4.27, S 10.08.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra.

Acknowledgments

The authors thank the Partenariat Hubert Curien (PHC) Franco-Portugais (programme PESSOA), the Université d'Orléans, the Universidade de Lisboa, the Spanish Ministerio de Economía y Competitividad (MINECO) [contract numbers SAF2010-15670, co-financed by the Fondos Europeos para el Desarrollo Regional (FEDER)] and the Fundación Ramón Areces for financial support. S. S. thanks Portuguese Fundação do Ministério de Ciência e Tecnologia (FCT) for the fellowship (SFRH/BD/16937/2004).

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Received: May 16, 2013
Published Online: October 9, 2013

