

Fused 1,3-oxazolidine-2-thiones on Ketohexose Backbones: Functional Modulation Processes

Arnaud Tatibouët*, Ana C. Simao and Patrick Rollin

ICOA - UMR 6005, Université d'Orléans, BP6759, F-45067 Orléans Cedex 2, France

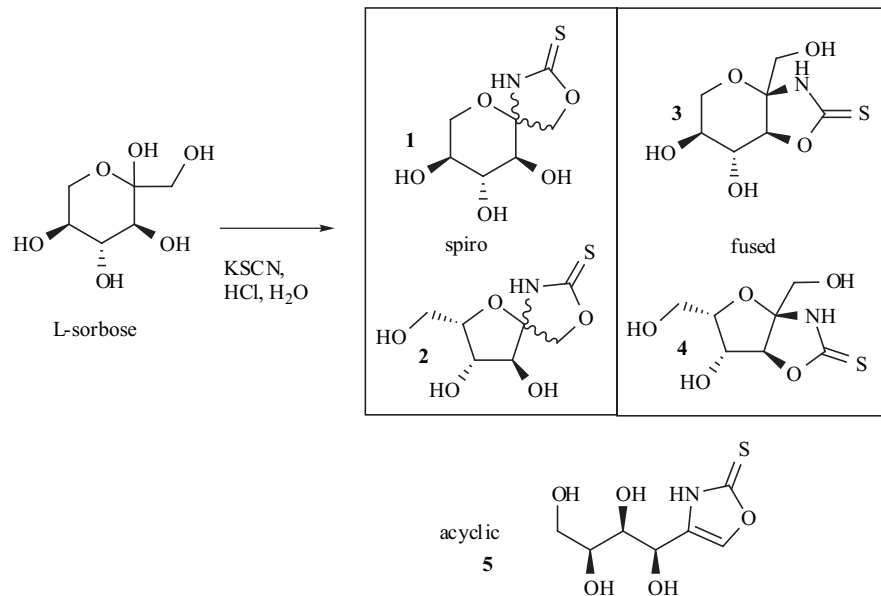
Received June 5, 2004; Accepted June 28, 2004

Abstract: 1,3-Oxazolidine-2-thiones fused to ketohexose backbone were prepared from 1-*O*-, 1-*N*- or 1-*S*-derivatives in reasonable yields. Spontaneous ring closure leads to *spiro*-tricyclic unexpected aminal and amide structures.

Keywords: 1,3-oxazolidine-2-thione, ketohexoses, L-sorbose, D-fructose.

1,3-Oxazolidine-2-thiones (OZT) based on carbohydrate templates are not so common structures - the main reason being that integrating such a cyclic thionocarbamate function in a saccharidic backbone is usually not a trivial operation [1]. Two major routes for the synthesis of carbohydrate OZT have previously been developed, involving either direct participation of the anomeric centre or preliminary replacement of one hydroxyl by an amino group. The latter approach implies nitrogen introduction, commonly through nucleophilic displacement and subsequent formation of the cyclic thionocarbamate by cooperative reaction of a *cis*-configured vicinal hydroxyl group with thiophosgene under basic conditions [2]. In contrast, the first approach involving the anomeric site is the oldest and also a more

appeared from earlier studies that direct reaction on free aldoses usually leads to furano structures with a perfect anomeric control, owing to the configuration of the neighbouring hydroxyl group [4]. We have initiated in recent years a re-examination of OZT formation at the anomeric site of carbohydrates aimed in particular at preparing nucleoside analogues or ketohexose mimics as inhibitors of GLUT5 - a D-fructose specific transmembrane transporter [5]. Complementary interest emerged when considering the number of possible structures **1-5** issued from the reaction of a ketohexose like L-sorbose with thiocyanic acid (Scheme 1). We have thus explored controlled elaborations for each structure and the possibilities of selective formation [6]. Moreover, ketohexose structures showing the most



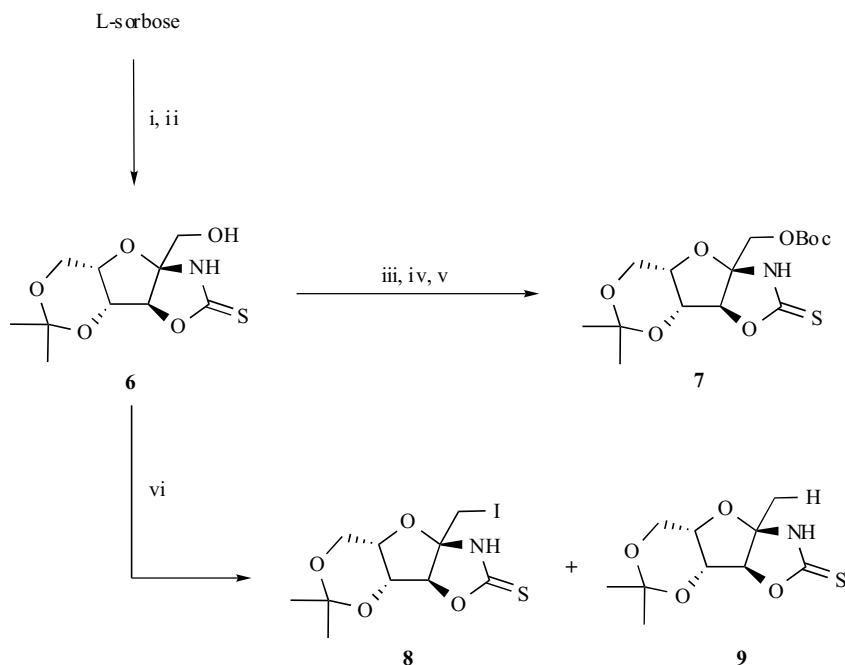
Scheme 1. Seven isomeric compounds can be obtained from L-sorbose.

straightforward one, only making use of KSCN under acidic conditions (*in situ* formation of thiocyanic acid) [3]. It

interesting inhibitory effects on GLUT5 transport of D-fructose called for functionalisation on the C-1 position [5b].

With a view to elaborating biochemical tools useful in studying GLUT5 properties, we have therefore tested some chemical modifications of this neopentyl position [7].

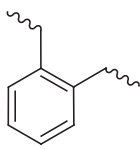
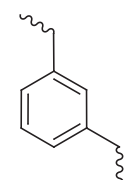
*Address correspondence to this author at the ICOA - UMR 6005, Université d'Orléans, BP6759, F-45067 Orléans Cedex 2, France; Tel.: +33-238-49-48-54; Fax: +33-238-41-72-81; E-mail: arnaud.tatibouet@univ-orleans.fr



Scheme 2. i- KSCN, HCl, H₂O. ii- acetone, cat. H₂SO₄. iii- TBDMSCl, imidazole, DMF. iv- (Boc)₂O, pyridine. v- TBAF, THF. vi- Garegg conditions: imidazole, Ph₃P, I₂, toluene.

Two approaches, either involving a *post*- or a *pre*-functionalisation, could be explored. The *post*-functionalisation was studied on the L-sorbo derivative **6**, easily available in two steps from L-sorbose in 50% overall

Table 1. 1-*O*-Alkylated OZT

carbohydrate	alkyl group R	alkylation	OZT formation
D-fructose	allyl	12a 100%	14a 64%
	benzyl	12b 94%	14b 71%
	CH ₂ CH(OMe) ₂	12c 90%	14c 61%
	CH ₂ CO ₂ Me	12d 85%	16 40%
L-sorbose	allyl	13a 94%	15a 65%
	benzyl	13b 96%	15b 81%
	CH ₂ CH(OMe) ₂	13c 75%	15c 45% ^a
	CH ₂ CO ₂ Me	13d 90%	17 47% ^b
	<i>ortho</i> -xylylene	13e 100%	15e 97%
	<i>meta</i> -xylylene	13f 100%	15f 98%

a- yield for a three-step sequence after acetylation.

b- yield for a three-step sequence after isopropylidenation.

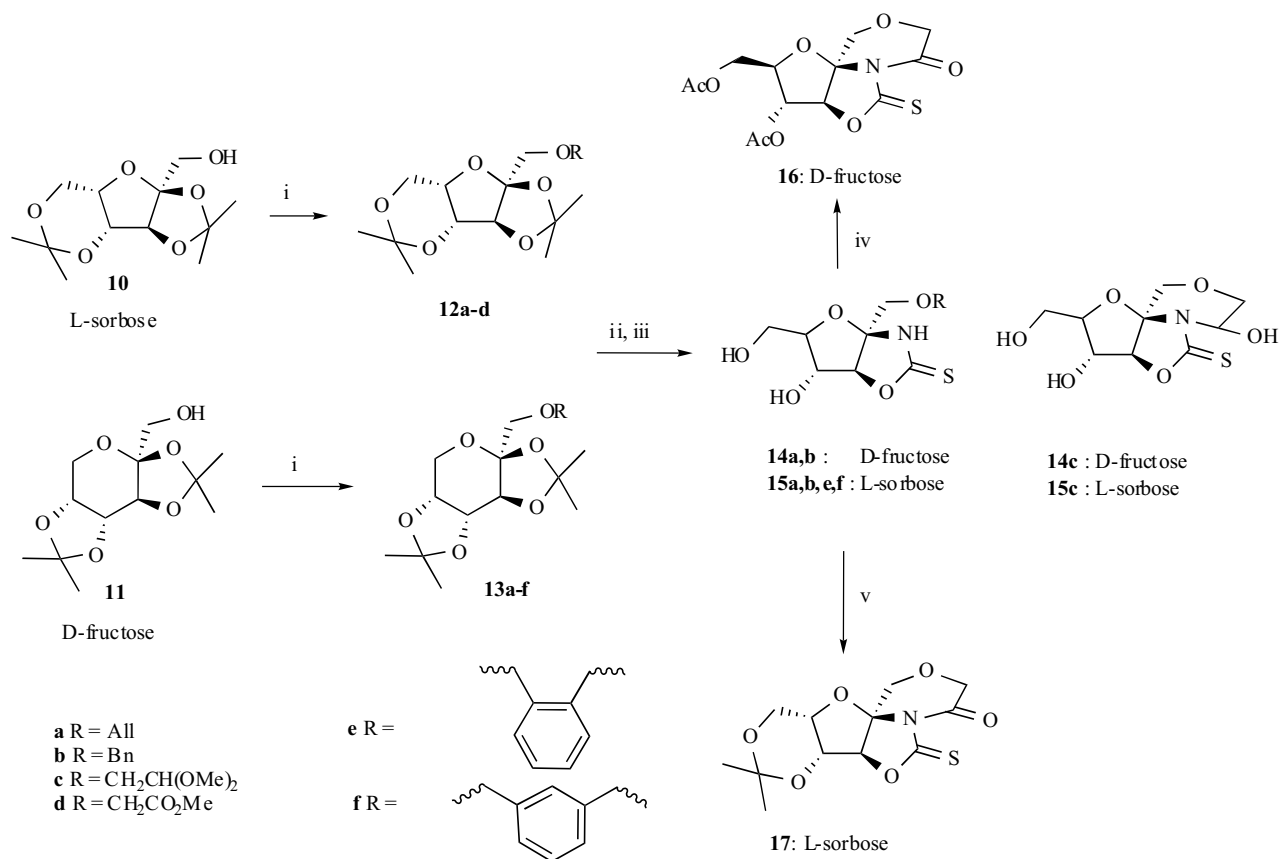
yield [5b]. A first attempt to selectively modify the C-1 position was undertaken through *O*-silylation then N-Boc protection on the OZT; unexpectedly however, selective deprotection of the TBDMS group resulted into migration of the Boc protection from the OZT nitrogen to O-1 (compound **7**). Direct functionalisation and regioselective halogenation through Mitsunobu reaction failed [8], while Garegg conditions [9] resulted in a mixture of the iodide **8** and the unexpected 1-deoxy derivative **9** in 35% and 33% yield, respectively.

As the *post*-functionalisation of OZT appeared somewhat deficient, the second approach was then considered much more attractive. We have previously taken advantage of *pre*-functionalisation in the selective preparation of ketohexose-fused OZT. *O*-1-Alkylation of ketohexoses can readily be achieved *via* a two-step sequence : di-*O*-isopropylidene formation to yield **10** [10] or **11** [11], then *O*-alkylation giving **12** or **13** in good yields (see Table 1).

Acid hydrolysis of the isopropylidene groups affords the 1-*O*-alkyl L-sorbo or D-fructo intermediates which can be condensed without purification with thiocyanic acid to yield efficiently the expected OZT **14** or **15**. We have successfully tested various monoalkylating reagents, as well as bis-alkylated α,α' dibromo *ortho*- and *meta*-xylenes in order to build up bio-relevant dimeric structures (Table 1, Scheme 3).

We could observe for OZT **14c**, **15c**, **16** and **17** a very particular behaviour. Indeed, formation of those OZT resulted in a spontaneous ring closure between the OZT-nitrogen site and the aldehyde or ester end of the O-1 appendage of the molecule. In the OZT synthetic process, a tricyclic structure is formed, displaying complex hemiaminal (**14c**, **15c**) or lactam (**16**, **17**) moieties (Scheme 3).

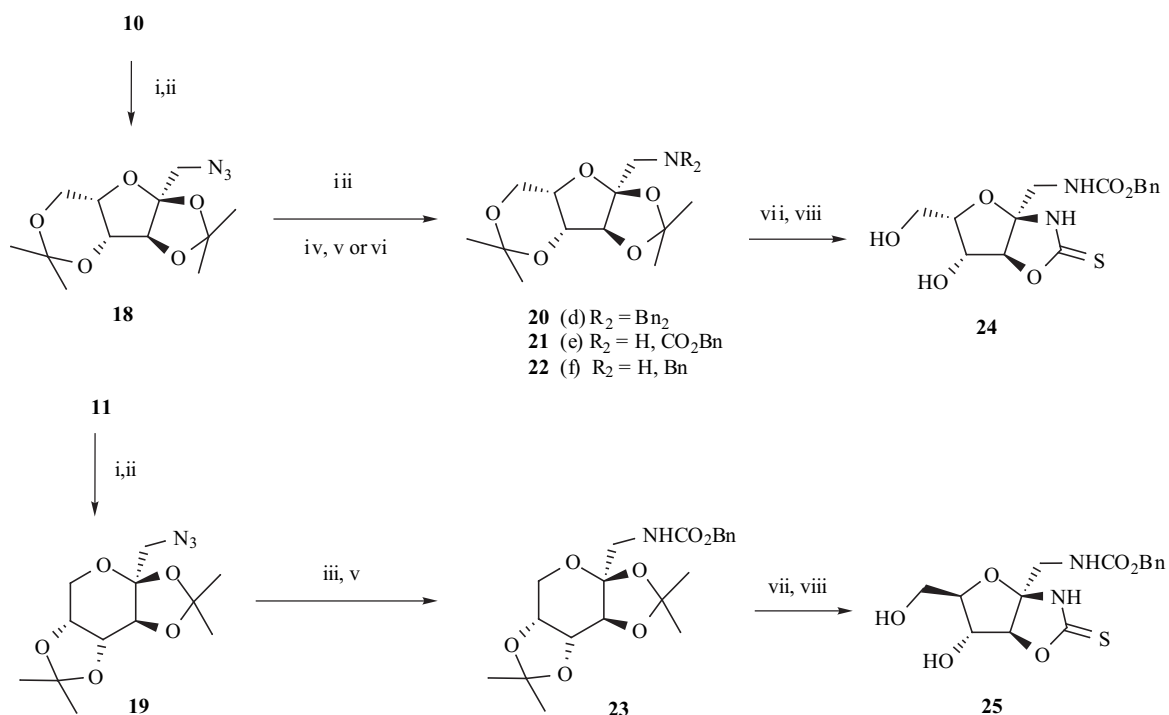
Introduction of another heteroatom in place of O-1 was also experimented. A nitrogen function could be introduced



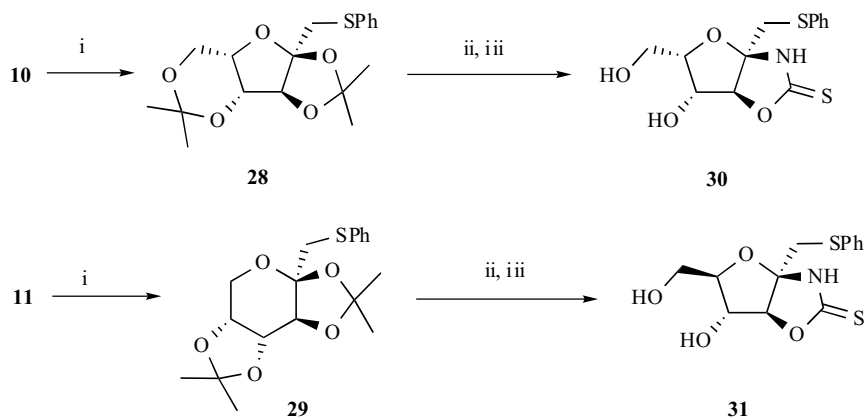
Scheme 3. i – NaH, RBr, DMF. ii- TFA-H₂O (7-3). iii- KSCN, HCl, H₂O. iv- Ac₂O, pyridine. v- acetone, cat. H₂SO₄.

at C-1 in ketohexose derivatives **10** and **11** through a two-step sequence involving Garegg's iodination conditions, then azido nucleophilic displacement with an overall yield of 80-85% for both primary azides **18** and **19** (Scheme 4). With

the object of having some comparison with oxygen derivatives, the Staudinger reaction was applied to **18** and **19**. After hydrolysis of the transient iminophosphorane, the resulting 1-amino-L-sorbo derivative was either *N,N*-



Scheme 4. i- Ph₃P, imidazole, I₂, toluene. ii- NaN₃, DMSO, 120°C. iii- Ph₃P, THF, H₂O. iv- NaH, DMF, BnBr. v- pyridine, BnOCOCl. vi - Ph₃P, PhCHO, THF, 24h then NaBH₃CN, EtOH. vii- TFA-H₂O (7-3). viii- KSCN, HCl, H₂O.



Scheme 5. a-(PhS)₂, (n-Bu)₃P, toluene, Δ. b- TFA-H₂O (7-3). c- KSCN, HCl, H₂O.

dibenzylated to yield **20** or protected with a benzyloxycarbonyl group to **21** – nearly quantitative yields were obtained in both cases. Furthermore, the transient iminophosphorane was also condensed with benzaldehyde to afford the benzylamino derivative **22** in 76% yield after reduction. Disappointingly, application of the final two-step sequence - TFA-H₂O (7-3) then KSCN, HCl, H₂O - on *N*-alkylated amines **20** and **22** or azide **18** did not produce any OZT. More satisfactory was the case of **21**, in which the benzylcarbamate group proved stable enough to allow the formation of the L-sorbo configured OZT **24** in 40% overall yield. Similarly, the 1-carbamoyl derivative **23** could be converted in 67% overall yield into the D-fructo configured OZT **25**.

A C-1 sulfur function was also introduced following a similar synthetic sequence (Scheme 5). Hata conditions (diphenyl disulfide, nBu₃P in toluene) were applied on di-*O*-isopropylidene ketohexoses **10** or **11**: the mild conditions usually effective for primary alcohols proved insufficient in those cases, most likely due to steric hindrance associated with neopentyl situations. Only refluxing of a toluene solution allowed the nucleophilic substitution to proceed, producing phenyl sulfides **28** and **29** in 95% and 67% yield respectively. Application of the final two-step sequence - TFA-H₂O (7-3) then KSCN, HCl, H₂O – resulted into rewarding 82% yield conversion of both **28** and **29** to provide L-sorbo and D-fructo configured OZT **30** and **31**.

In summary, fused OZT on keto-hexose backbones can readily be obtained from 1-*O*-alkylated derivatives *via* a highly selective short sequence giving furano structures whose anomeric configurations are directed by the 3-OH group. Moreover, a subsequent spontaneous ring closing process can occur when electrophilic functions such as aldehyde or ester are present on the O-1 side chain. The general process was also successfully applied to C-1 nitrogen- or sulfur-functionalized ketohexose derivatives. Those simple synthetic sequences open the way to diversely functionalized and totally defined furano templates which

will be used to elaborate ketohexose biomimetics to study their biological transporters (GLUTs).

ACKNOWLEDGEMENTS

The authors wish to thank the CNRS and the Université d'Orléans for financial support.

REFERENCES AND NOTES

- [1] (a) Garcia Fernandez, J. M.; Ortiz Mellet, C. *Sulfur Reports* **1996**, *19*, 61-169; (b) Garcia Fernandez, J. M.; Ortiz Mellet, C. *Adv. Carbohydr. Chem. Biochem.* **2000**, *55*, 35-135.
- [2] (a) Garcia Fernandez, J. M.; Ortiz Mellet, C.; Fuentes, J. *Tetrahedron Lett.* **1992**, *33*, 3931-3934; (b) Garcia Fernandez, J. M.; Ortiz Mellet, C.; Jimenez Blanco, J. L.; Fuentes, J. *J. Org. Chem.* **1994**, *59*, 5565-5572; (c) Benito, J. M.; Gomez-Garcia, M.; Jimenez Blanco, J. L.; Ortiz Mellet, C.; Garcia Fernandez, J. M. *J. Org. Chem.* **2001**, *66*, 1366-1372; (d) Garcia-Moreno, M. I.; Diaz-Perez, P.; Ortiz Mellet, C.; Garcia Fernandez, J. M. *J. Org. Chem.* **2003**, *68*, 8890-8901.
- [3] (a) Zemplén, G.; Gerecs, A.; Rados, M. *Ber.* **1936**, *39*, 748-754; (b) Bromund W. H.; Herbst, R. M. *J. Org. Chem.* **1945**, *10*, 267-276.
- [4] (a) Wickstrom, A.; Wold, J. K. *Acta Chem. Scand.* **1959**, *13*, 1129-1136; (b) Jochims, J. C.; Seeliger, A.; Taigel, G. *Chem. Ber.* **1967**, *100*, 845-854.
- [5] (a) Girniene, J.; Apremont, G.; Tatibouët, A.; Sackus, A.; Rollin, P. *Tetrahedron* **2004**, *60*, 2609-2619; (b) Girniene, J.; Tatibouët, A.; Sackus, A.; Yang, J.; Holman, G. D.; Rollin, P. *Carbohydr. Res.* **2003**, *338*, 711-719.
- [6] (a) Grouiller, A.; Mackenzie, G.; Najib B.; Shaw, G.; Ewig, D. *Chem. Commun.* **1998**, 671-672; (b) Lichtenthaler, F.W.; Klotz, J.; Flath F.-J. *Liebigs Ann.* **1995**, 2069-208; (c) Tatibouët, A.; Lawrence, S.; Rollin, P.; Holman, G. D. *Synlett* **2004**, submitted.
- [7] Yang, J.; Dowden, J.; Tatibouët, A.; Hatanaka Y.; Holman, G. D. *Biochem. J.* **2002**, *367*, 533-539.
- [8] Lohray, B. B.; Sekkar Reddy, A.; Bhushan, V. *Tetrahedron: Asymmetry* **1996**, *7*, 2411-2416.
- [9] Garegg, P. J.; Samuelsson, B. *J. Chem. Soc. Chem. Commun.* **1979**, 979-980.
- [10] Crawford, T. C.; Crawford, S. A. *Adv. Carbohydr. Chem. Biochem.* **1980**, *37*, 92-96.
- [11] Brady Jr., R. F. *Carbohydr. Res.* **1970**, *15*, 35-40.