

Preliminary Studies on the Transformation of Nitrosugars into Branched Chain Iminosugars: Synthesis of 1,4-Dideoxy-4-C-hydroxymethyl-1,4-imino-pentanol

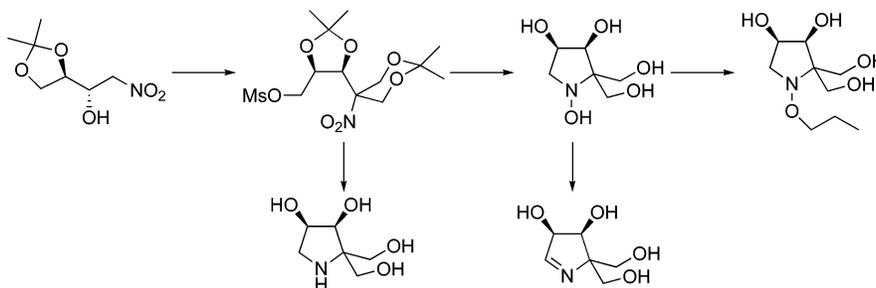
José M. Otero,[†] Raquel G. Soengas,[‡] Juan C. Estévez,[†] Ramón J. Estévez,^{*,†}
David J. Watkin,[‡] Emma L. Evinson,[§] Robert J. Nash,[§] and George W. J. Fleet[‡]

Departamento de Química Orgánica, Universidade de Santiago, 15782 Santiago de Compostela, Spain, Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K., and Institute of Grassland and Environmental Research, Plas Gogerddan, Aberystwyth SY23 3EB, Wales, U.K.

qorjec@usc.es

Received November 28, 2006

ABSTRACT



A novel promising strategy for the transformation of nitrosugars into branched pyrrolidines, based on double Henry reaction with formaldehyde followed by reductive ring closure, allowed the first enantiospecific synthesis of a 4-C-hydroxymethyl branched derivative of the well-known glycosidase inhibitor 1,4-dideoxy-1,4-imino-pentanol. This strategy also afforded a new route to some other interesting derivatives, such as N-hydroxy, N-propyloxy, and imino derivatives, a new kind of compounds with promising biological properties.

Glycosidases are involved in several important biological processes such as digestion, the biosynthesis of glycoproteins, and the catabolism of glycoconjugates. Analogues of furanoses in which the ring oxygen is replaced by nitrogen and the anomeric hydroxyl is removed have been reported to be almost always inhibitors of the corresponding glycosidases.¹ Because glycosidase inhibitors have the potential to produce

antiviral, antidiabetic, and anticancer effects as well as immune modulatory properties,² they have attracted much attention.³

Polyhydroxylated pyrrolidines are among the most active glycosidase inhibitors.^{2a,4} This includes several isomers of

(2) (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (b) Somsak, L.; Nagy, V.; Hadady, Z.; Docsa, T.; Gergely, P. *Curr. Pharm. Design* **2003**, *9*, 1177.

(3) (a) Ayad, T.; Genisson, Y.; Broussy, S.; Baltas, M.; Gorrichon, L. *Eur. J. Org. Chem.* **2003**, *15*, 2903. (b) Lee, B. W.; Jeong, I. Y.; Yang, M. S.; Choi, S. U.; Park, K. H. *Synthesis* **2000**, *9*, 1305.

(4) *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Stutz, A. E., Ed.; Wiley-VCH: Weinheim, 1999.

[†] Universidade de Santiago.

[‡] University of Oxford.

[§] Institute of Grassland and Environmental Research.

(1) Asano, N.; Oseki, K.; Kiuz, H.; Matsui, K. *J. Med. Chem.* **1994**, *37*, 3701.

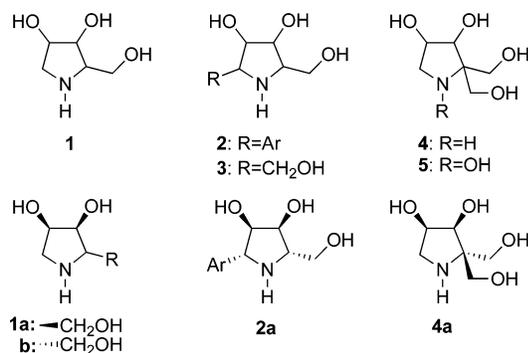


Figure 1. 1,4-Dideoxy-1,4-imino-pentanol derivatives.

iminosugar **1** (Figure 1),⁵ such as natural imino-D-ribose.⁶ Moreover, derivatives of compounds **1** provide an opportunity for altering and hopefully increasing the specificity of inhibition of individual glycosidases. Thus, derivatives such as **2**, bearing an aromatic group at position C-1, are purine nucleoside phosphorylase (PNPase) inhibitors,⁷ and derivatives such as **3**, analogues of **1** substituted at the C-1 position, have also been reported as powerful and specific glycosidase inhibitors.⁸ Accordingly, it is of interest to prepare families of branched pyrrolidine iminosugars **4** and **5**, analogues of **1**, to test their activity against a range of glycosidases and hence to know how the introduction of a branch in different ring positions can alter the inhibitory activity.⁹ The carbon branched pyrrolidine **4a** may be considered as a 4-C-hydroxymethyl analogue of the imino-D-lyxitol **1a**, a powerful α -galactosidase inhibitor.^{2a} Removal of the diastereotopic hydroxymethyl group in **4a** would allow it to be considered as an imino-L-ribose **1b**.¹⁰ Derivative **2a** with an aromatic substituent is a potent inhibitor of PNPases.¹¹

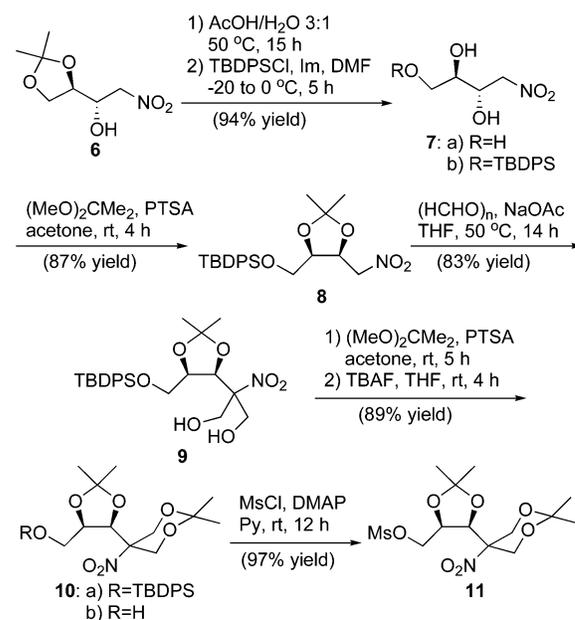
Nitrosugars are powerful synthetic materials because they combine the synthetic potential of sugars and the chemical versatility of the nitro group;¹² the nitroaldol condensation (the Henry reaction) is a classical method for the construction

of carbon–carbon bonds.¹³ After the carbon framework has been set up, the nitro group can be converted into a range of other functionalities.¹⁴

As a continuation of our present interest on new synthetic applications of nitrosugars,¹⁵ herein we describe the first enantiospecific synthesis of azafuranose **4a**, which includes the early introduction of its two hydroxymethyl substituents at C-4 of a nitrosugar by a double Henry condensation with formaldehyde. In the course of our studies, the *N*-hydroxypyrrolidine **5a** was also obtained.

Nitro compound **6**, easily prepared from D-mannitol,¹⁶ was treated with aqueous acetic acid to afford the corresponding trihydroxynitro compound **7a**. Selective protection of its primary hydroxyl group as *t*-butyldiphenylsilyl ether, followed by protection of the resulting diol **7b** by reaction with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in acetone, provided the key isopropylidene nitro derivative **8** (Scheme 1). The double condensation of nitro compound **8** with

Scheme 1. Synthesis of Linear Branched Nitroderivative Precursor **11**



formaldehyde was achieved by using paraformaldehyde as the source of the two hydroxymethyl groups. After protection of the dihydroxymethyl system of **9** by reaction with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in acetone, treatment of diacetone derivative **10a** with tetrabutylammonium fluoride gave the expected nitroalcohol **10b**, which was transformed into mesylate **11** by reaction with mesyl chloride in pyridine.

(5) (a) Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymmetry* **1990**, *1*, 119. (b) Behling, J. R.; Campbell, A. L.; Babiak, K. A.; Neg, J. S.; Medich, J.; Farid, P.; Fleet, G. W. J. *Tetrahedron* **1993**, *49*, 3359. (c) Fleet, G. W. J.; Nicholas, S. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1985**, *26*, 3127.

(6) Mizushima, Y.; Xu, X.; Asano, N.; Kasai, N.; Kato, A.; Takemura, M.; Asahara, H.; Linn, S.; Sugawara, F.; Yoshida, H.; Sakaguchi, K. *Biochem. Biophys. Res. Commun.* **2003**, *304*, 78.

(7) (a) Yu, C.-Y.; Mu-Hua, H. *Org. Lett.* **2006**, *8*, 3021. (b) Schramm, V. L.; Tyler, P. C. *Curr. Top. Med. Chem.* **2003**, *3*, 525. (c) Ringia, E. A. T.; Tyler, P. C.; Evans, G. B.; Furneaux, R. H.; Murkin, A. S.; Schramm, V. L. *J. Am. Chem. Soc.* **2006**, *128*, 7126.

(8) Yu, C.-Y.; Asano, N.; Ikeda, K.; Wang, M.-X.; Butters, T. D.; Wormald, M. R.; Dwek, R. A.; Winters, A. L.; Nash, R. J.; Fleet, G. W. J. *Chem. Commun.* **2004**, *17*, 1936.

(9) For preliminary work in this field, see: (a) Blanco, M. J.; Sardina, F. J. *J. Org. Chem.* **1998**, *63*, 3411. (b) Burley, I.; Hewson, A. T. *Tetrahedron Lett.* **1994**, *35*, 7099. (c) Bols, M. *Tetrahedron Lett.* **1996**, *37*, 2097.

(10) Fleet, G. W. J.; Son, J. C.; Green, D. S. C.; di Bello, I. C.; Winchester, B. *Tetrahedron* **1988**, *44*, 2649.

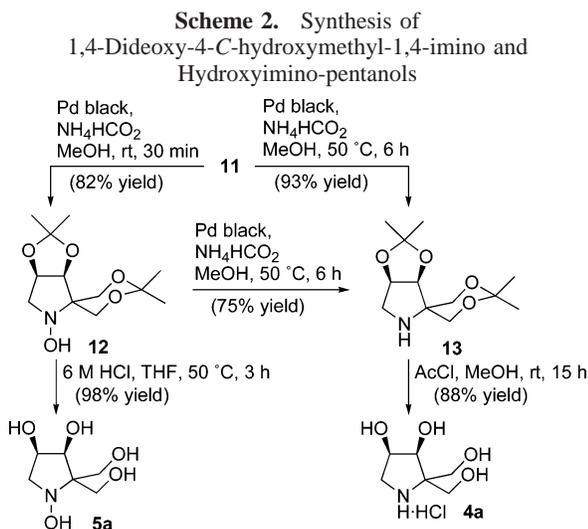
(11) Clinch, K.; Evans, G. B.; Fleet, G. W. J.; Furneaux, R. H.; Johnson, S. W.; Lenz, D.; Mee, S.; Rands, P. R.; Schramm, V. L.; Ringia, E. A. T.; Tyler, P. C. *Org. Biomol. Chem.* **2006**, *4*, 1131.

(12) (a) Barret, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751. (b) *Nitroalkanes and Nitroalkenes in Synthesis*; Tetrahedron Symposia; Barret, A. G. M., Ed.; 1990; Vol. 46, p 7313. (c) Noboru, O. In *The Nitro Group in Organic Synthesis*; Feuer, H., Ed.; Organic Nitro Chemistry Series; Wiley-VCH: New York, 2001.

(13) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.

(14) (a) Pinnick, H. W. *Org. React.* **1990**, *38*, 655. (b) McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259. (c) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367.

According to our synthetic plan, reduction of the nitro group of compound **11** and subsequent ring closure would provide the pyrrolidine ring of compound **13** (Scheme 2).



The nitro group of **11** was stable under many of the usual reduction conditions attempted, but finally treatment of **11** with palladium black and ammonium formate at room temperature resulted in a tandem reaction corresponding to the partial reduction of the nitro group to a hydroxylamine followed by a spontaneous ring closure, affording the *N*-hydroxyiminosugar derivative **12** instead of the expected **13**. The structure of **12** was unambiguously established by X-ray crystallographic analysis (Figure 2).¹⁷ Amine **13** was obtained when the above reduction of **11** was carried out at 50 °C and also when **12** was subjected to the same reaction conditions. Finally, removal of the two isopropylidene groups of **12** under acidic conditions gave branched *N*-hydroxyiminosugar **5a**. Compound **13** was similarly converted into the target branched iminosugar **4a**, which was isolated as its hydrochloride salt. The spectroscopic properties of compound **4a**, the hydrochloride of which had $[\alpha]_D^{23} -5.2$ (*c*, 1.30 MeOH), were identical to those previously reported for racemic **4a**.¹⁸

Recently, some *O*-alkylated-*N*-hydroxy derivatives of known pyranose glycosidase inhibitors were synthesized and

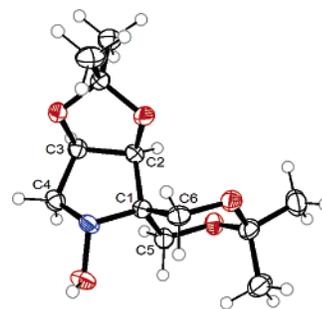
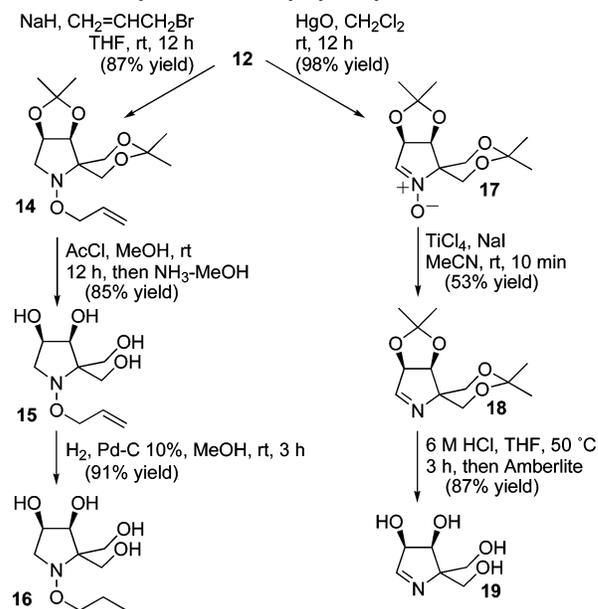


Figure 2. Molecular structure of compound **12** in the solid state.

shown to be inhibitors of glycosidases.¹⁹ This encouraged us to study the *O*-alkylation of *N*-hydroxylamine **12**.

The *O*-alkylated derivative **16** was readily obtained by treatment of **12** with 3-bromopropene and sodium hydride to give the allyl hydroxylamine **14**; subsequent acid hydrolysis of **14** afforded **15** which on catalytic hydrogenation gave the propyl derivative **16** (Scheme 3).

Scheme 3. Synthesis of Alkylhydroxyl and Imino Derivatives



Hydroxylamine **12** was additionally transformed into imino derivative **19**, a branched analogue of nectrisine (FR900483) and similar well-known glycosidase inhibitors.²⁰ Oxidation of **12** with mercury oxide²¹ and subsequent reaction of the

(15) (a) Otero, J. M.; Fernández, F.; Estévez, J. C.; Estévez, R. J. *Tetrahedron: Asymmetry* **2005**, *16*, 4045. (b) Otero, J. M.; Barcia, J. C.; Estévez, J. C.; Estévez, R. J. *Tetrahedron: Asymmetry* **2005**, *16*, 11. (c) Soengas, R. G.; Pampín, M. B.; Estévez, J. C.; Estévez, R. J. *Tetrahedron: Asymmetry* **2005**, *15*, 211. (d) Soengas, R. G.; Estévez, J. C.; Estévez, R. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3955. (e) Soengas, R. G.; Estévez, J. C.; Estévez, R. J. *Org. Lett.* **2003**, *5*, 4457. (f) Soengas, R. G.; Estévez, J. C.; Estévez, R. J.; Maestro, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1653. (g) Soengas, R. G.; Estévez, J. C.; Estévez, R. J. *Org. Lett.* **2003**, *5*, 1423.

(16) (a) Choudary, B. M.; Sarma, M. R.; Prasad, A. D.; Narender, N. *Indian J. Chem.* **1994**, *33*, 152. (b) LeCocq, J.; Ballou, C. E. *Biochemistry* **1964**, *3*, 976. (c) Kozikowski, A. P.; Kitagawa, Y.; Springer, J. P. *J. Chem. Soc., Chem. Commun.* **1983**, *23*, 1460.

(17) Crystallographic data for the structure of compound **12** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-628982. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax (+44)1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

(18) Schieweck, F.; Altenbach, H.-J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3409.

(19) Sun, L.; Li, P.; Landry, D. W.; Zhao, K. *Tetrahedron Lett.* **1996**, *37*, 1547.

(20) (a) Shibata, T.; Nakayama, O.; Tsurumi, Y.; Okuhara, M.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1988**, *41*, 296. (b) Kayakiri, H.; Takase, S.; Setoi, H.; Uchida, I.; Terano, H.; Hashimoto, M. *Tetrahedron Lett.* **1988**, *29*, 1725. (c) Tsujii, E.; Muroi, M.; Shiragami, N.; Takatsuki, A. *Biochem. Biophys. Res. Commun.* **1996**, *220*, 459.

resulting nitrene **17** with titanium tetrachloride and sodium iodide provided a protected imino derivative **18**,²² which was directly subjected to exhaustive acidic hydrolysis to yield the desired imino compound **19** as the major component of an unseparable reaction mixture.²³

Evaluation of the activity of derivatives **4a**, **15**, **16**, and **19** as glycosidase inhibitors is currently in progress. Preliminary results compare the glycosidase inhibition at 0.8 mM (Table 1). It is interesting to note that **4a** is a potent

Table 1. Inhibition of Glycosidases by Compounds **4a**, **15**, **16**, and **19**

enzyme (source)	% inhibition			
	4a	15	16	19
α -glucosidase (yeast)	0	3	0	3
α -glucosidase (<i>Bacillus</i>)	52	5	15	21
α -glucosidase (rice)	0	0	0	-12
β -glucosidase (almond)	0	0	0	0
α -galactosidase (coffee bean)	76	-11	48	10
β -galactosidase (bovine liver)	3	12	40	80
α -fucosidase (bovine kidney)	35	0	0	0
α -mannosidase (Jack bean)	0	6	0	0
β -mannosidase (<i>Cellulomonas</i>)	6	0	0	0
naringinase (<i>Penicillium</i>)	0	0	7	22
β - <i>N</i> -acetylglucosaminidase (bovine kidney)	-9	5	0	0
β - <i>N</i> -acetylglucosaminidase (Jack bean)	6	0	0	0
β - <i>N</i> -acetylglucosaminidase (<i>Aspergillus</i>)	-11	0	-7	0

inhibitor of the α -galactosidase, but **19** potently inhibits the β -galactosidase. IC_{50} and K_i values need to be determined, but both compounds appear to show interesting specificity. **16** is a weak but nonetheless quite specific inhibitor of galactosidases. These compounds should be evaluated as potential chaperones for lysosomal storage disorders caused by a deficiency in lysosomal acidic α -galactosidase.

In summary, a promising strategy has been developed for the enantiospecific synthesis of branched polyhydroxylated pyrrolidines that allows access to enantiopure pyrrolidines

(21) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5724.

(22) Balicki, R. *Chem. Ber.* **1990**, *123*, 647.

4a, **5a**, **16**, and **19** from nitrosugar **6**. This new route, based on the powerful synthetic utility of nitrosugars, includes a key step consisting of double nitroaldol condensation with formaldehyde, followed by a one-pot reductive ring closure of the resulting nitro derivative **11**.

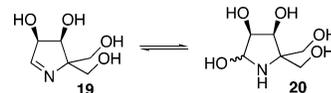
The synthetic methodology presented here may have considerable scope. Accordingly, work is now in progress aimed at its application to the plethora of 5-deoxy-5-nitro-hexofuranoses to access the whole families of stereoisomers of iminosugars **4a**, **15**, **16**, and **19** for biological evaluation. Our future plans include extending these chemical and biological studies to the panel of 6-deoxy-6-nitro-hexofuranoses to give rise to a great variety of novel 1-C-hydroxy-methyl derivatives of polyhydroxylated piperidines and polyhydroxylated azepanes of well-known inhibitory activity such as the natural 1-deoxynojirymicin,²⁴ homonojirymicins,²⁵ and nojirymicin homologues.²⁶

Acknowledgment. We thank the Spanish Ministry of Education and Science for financial support and for a FPU grant to José M. Otero.

Supporting Information Available: General experimental procedures for compounds **7b**, **8**, **9**, **10a**, **10b**, **11–13**, **5a**, **4a**, and **14–19** and characterization data for all products, together with preliminary glycosidase screening of compounds **4a**, **15**, **16**, and **19**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL062887V

(23) Acidic hydrolysis of iminoderivative **18** provided an unseparable mixture, which was assigned as an equilibrium mixture of target **19** (major component) and its hydrated derivative **20** (minor component).



This mixture was used for bioassay without further purification. For similar previous results, see: (a) Joubert, M.; Defoin, A.; Tarmus, C.; Streith, J. *Synlett* **2000**, 1366. (b) Kim, Y. J.; Takatsuki, A.; Kogoshi, N.; Kitahara, T. *Tetrahedron* **1999**, *55*, 8353.

(24) Tite, T.; Lallemand, M.-C.; Poupon, E.; Kunesch, N.; Tillequin, F.; Gravier-Pelletier, C.; Le Merrer, Y.; Husson, H.-P. *Bioorg. Med. Chem.* **2004**, *12*, 5091.

(25) Martin, O. L.; Saavedra, O. M.; Xie, F.; Liu, L.; Picasso, S.; Vogel, P.; Kizu, H.; Asano, N. *Bioorg. Med. Chem.* **2001**, *9*, 1269.

(26) Li, H.; Schuzt, C.; Favre, S.; Zhang, Y.; Vogel, P.; Sinay, P.; Blériot, Y. *Org. Biomol. Chem.* **2006**, *4*, 1653.