doi:10.2533/chimia.2011.40 Chimia 65 (2011) 40–44

Syntheses and Biological Activities of 1,4-Iminoalditol Derivatives as α-L-Fucosidase Inhibitors

Elena Moreno-Clavijo, Ana T. Carmona*, Antonio J. Moreno-Vargas, Lidia Molina, and Inmaculada Robina*

Abstract: A review dealing with 1,4-iminoalditol (hydroxylated pyrrolidine) derivatives as inhibitors of α-L-fucosidases including the different synthetic approaches for their preparation as well as their inhibitory properties is presented.

Keywords: Fucosidases · Glycosidase inhibitors · Iminosugars · Pyrrolidines

1. Introduction

α-L-Fucosidases are exo-glycosidases involved in the last stages of glycoprotein biosynthesis, catalyzing the hydrolysis of the terminal α-L-fucose residues contained in the cell surface oligosaccharides *via* 1,2, 1,3-, 1,4- or 1,6-linkages,[1] and participating in a variety of biological processes.[2] These enzymes, like other glycosidases, are able to catalyze glycosylation reactions since glycosylation processes and hydrolysis are reversible and, in consequence, α-L-fucosidases can also be used in the synthesis of fucosylated glycans.[3] The accumulation of glycoconjugates containing fucose due to the absence or deficiency of α-L-fucosidases, induces the recognition of the α-L-fucose moieties by specific lectins that lead to neurovisceral disorders known as fucosidosis.[4] An abnormal α-L-fucosidase distribution, both extracellular and intracellular, is found in inflammation,[5] cystic fibrosis,[6] tumor cell growth and metastasis.[7] Moreover, α-L-fucosidases are used as diagnostic markers for the early detection of several carcinomas.[8] α-L-Fucosidases are also present in the membranes of human sperm cells and facilitate sperm transport and sperm-egg interactions, so that their inhibitors may have contraceptive properties.[9]

Due to the variety and importance of the biological processes that involve α-L-fucosidases, the amount of structural data in the literature on this enzyme is increasing.[10,11] Several enzyme–inhibitor complexes have been crystallized. In 2004 Bourne and coworkers studied the complex between α-L-fucosidase from the bacteria *Thermotoga maritima* and the 2-deoxy-2-fluorofucopyranosyl fluoride[12] and, in 2007, Kato and coworkers that of the α-L-fucosidase isolated from *Bifidobacterium bifidum* with deoxyfuconojirimycin.[13] Recently, Lin, Wang and coworkers[14] reported the X-ray crystal structures of nine complexes between α-L-fucosidase from *Thermotoga maritima* (TmF) and iminocyclitols bearing hydrophobic side chains.

Inhibitors of α-L-fucosidases can be used as probes for the study of these enzymes with regard to their function and for the development of potential therapeutic agents. This enzyme is necessary in the processes of glycosylation of the viral envelope, which is essential in the formation of mature virus. Some of the α-L-fucosidase inhibitors also inhibit the cytopathic effect of HIV and reduce infection.[15] Although a large number of glycosidase inhibitors can be used to alleviate diseases, the development of effective drugs based on them without side effects has been difficult to achieve. This is partly because many enzyme inhibitors, both natural and synthetic, are active against more than one enzyme resulting in the appearance of side effects. It would be possible to obtain more selective inhibitors with a deeper knowledge of structure-activity relationships and a better understanding of the mechanism of action of glycosidases, together with a detailed structural design. This process is complicated because only a small number of existing glycosidases has been cloned and overexpressed.[16] Therefore, the search for not only effective but also selective α-L-fucosidase inhibitors is a field of current interest.

The aim of this review is to present a compilation of the existing 1,4-iminoalditols as inhibitors of α-L-fucosidases to date. The different synthetic strategies employed in their preparation as well as their inhibitory properties are also presented.

2. Polyhydroxylated Pyrrolidines

Polyhydroxylated pyrrolidines or 1,4-iminoalditols are a type of well-known glycosidase inhibitors. Their inhibitory properties are enhanced if the iminosugar, which mimics the pyranosyl cation, includes some information of the aglycon undergoing the hydrolytical process.[17] It has been reported that hydrophobic groups attached to the iminosugar improve their inhibitory activity by contributing with non-specific binding stabilizing interactions to the enzyme, and/or with the elimination of water molecules in the hydrophobic active site, thereby increasing the affinity of the enzyme to the inhibitor due to the entropy released in the process.[18] We have reported[19] that the inhibitory properties of the weak and non-selective glycosidase inhibitor *meso*-pyrrolidine-3,4-diol (**1**) can be significantly improved by joining aromatic and heteroaromatic moieties to the pyrrolidine framework. Thus, polyhydroxylated pyrrolidines having a (2*S*/*R*,3*S*,4*R*) configuration and incorporating a furan ring at position C(2) of the iminosugar, are more potent and spe-

*Correspondence: Dr. A. T. Carmona, Dr. I. Robina
Dept. Organic Chemistry
Faculty of Chemistry
University of Seville
P.O. Box 1203, E-41071 Seville, Spain
Tel.: +34 954 556 858
Fax: +34 954 624 960
E-mail: anatere@us.es; robina@us.es

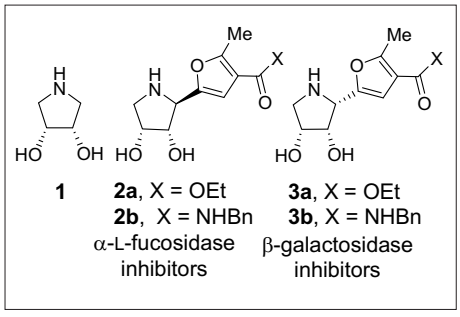
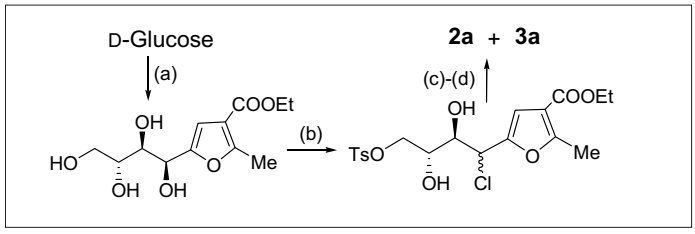


Fig. 1. Enzymatic inhibitory activities of **1**–**3**.



Scheme 1. Reagents and conditions: (a) Ethyl acetoacetate, $ZnCl_2$. (b) (1) TsCl/Py, (2) NCS, SMe, DCM, –20 °C, 50%. (c) (1) NaN_3/DMF, (2) H_2, Pd-C, (3) CbzCl, $NaHCO_3$ aq., (4) Ac_2O/ Py, (5) Chromatographic separation, 60% (4 steps). (d) (1) NaOMe/MeOH, (2) H_2, Pd-C, EtOH.

cific inhibitors than *meso*-pyrrolidine **1**. Moreover, they show a drastic dependence of the specificity with the configuration of pseudo-anomeric center C(2). Thus, [(2*R*,3*S*,4*R*)-3,4-dihydroxypyrrolidin-2-yl]furan derivatives (**2a**, **2b**) are good α-L-fucosidase inhibitors (human placenta) [*i.e.* **2b**, K_i = 2.2 μM] whereas their C(2) epimers (**3a**, **3b**) exhibit specific inhibition towards β-galactosidase (jack beans) [*i.e.* **3a**, K_i = 6.4 μM] (Fig. 1).[20]

The preparation of **2a** and **3a** was carried out starting from a polyhydroxyalkyl furan, easily obtained from D-glucose, through a double functionalization of the side chain and subsequent nucleophilic internal displacement (Scheme 1).[20]

Polyhydroxylated pyrrolidines having a methyl group at C(5) and L-*fuco* configuration, have shown remarkable inhibitory activities towards α-L-fucosidases because of their similarity to the fucopyranosyl cation originated in the hydrolysis of an *O*-fucopyranoside. Derivatives **4**, **5**,[21,22] **6**,[23] and **7**,[21,22] have proven to be inhibitors of α-L-fucosidases in the nanomolar range (Fig. 2).

Pyrrolidine amino-L-lyxose **4** was prepared as indicated in Scheme 2. Reduction of nitrone **8**, easily obtained from D-ribose,[21a,24] with aqueous SO_2 gave crystalline sulfite adduct **9**. The aminosugar **4** was obtained by SO_2-elimination with $Ba(OH)_2$.[21a]

The synthesis of **4** and **5** was carried out by Wong and coworkers starting from primary tosylate **10**, which was obtained from D-ribose (Scheme 3).[22] Compound **5** was also prepared in seven steps and 33% overall yield from D-ribose following Jäger's methodology.[24] This strategy implied the halocyclization of unsaturated oximes, easily obtained from D-sugars (Scheme 4).

Compound **6** was prepared by Wong and coworkers[25] through a chemo-enzymatic synthesis from azidocarbaldehyde **11** and dihydroxyacetone-3-phosphate (DHAP) in the presence of Fuc-1-P aldolase (Scheme 5).

The preparation of compound **7** was performed by a 1,3 dipolar cycloaddition of nitrone **8** with alkene **13a** as key step (Scheme 6).[21a]

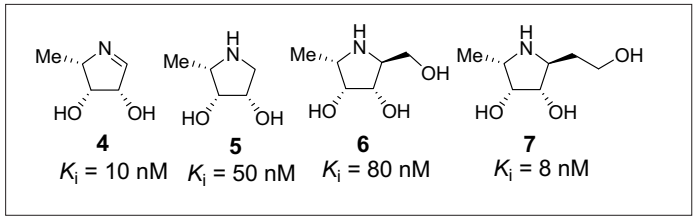
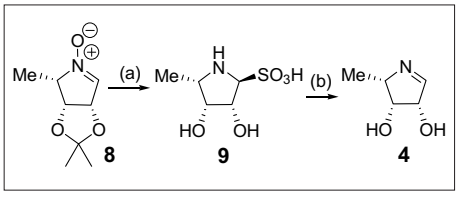
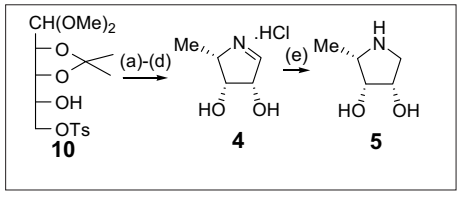


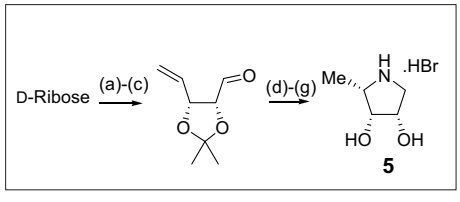
Fig. 2. Inhibitory activities of **4**–**7** towards α-L-fucosidases from bovine kidney.



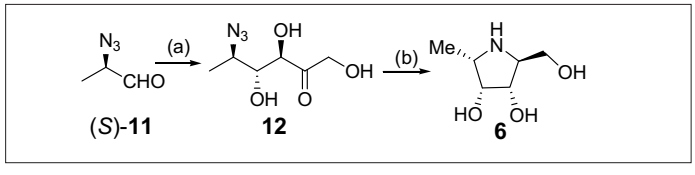
Scheme 2. Reagents and conditions: (a) SO_2/ H_2O, 62%. (b) $Ba(OH)_2$.



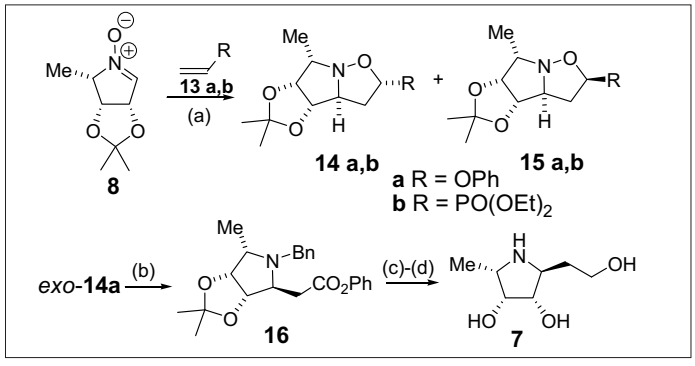
Scheme 3. Reagents and conditions: (a) NaN_3, DMF, 80 °C, 86%. (b) (1) PPh_3, $PhCH_3$, reflux, (2) *p*-TsCl, Et_3N, CH_2Cl_2, 100%. (c) (1) Red-Al, THF, (2) Na, NH_3, THF, 88%. (d) MeOH, 1 N HCl, 100%. (e) $NaCNBH_3$, MeOH, 12%.



Scheme 4. Reagents and conditions: (a) $Me_2CO/Me_2C(OMe)_2$, MeOH, HCl, 70%. (b) I_2, PPh_3, 70 °C, imidazole, toluene. (c) BuLi, THF, –80 °C, 90%. (d) $NH_2OH.HCl$, Na_2CO_3, EtOH/ H_2O, 90%. (e) Br_2, $NaHCO_3$, CH_2Cl_2, 0–25 °C, MPLC (83:17). (f) H_2 (3 bar), Pd/C, MeOH, 92%. (g) HBr, MeOH, 95%.



Scheme 5. Reagents and conditions: (a) DHAP/Fuc-1-P aldolase, then acid phosphatase, 10%. (b) H_2/Pd-C, 50 psi, 76%.



Scheme 6. Reagents and conditions: (a) C_2Cl_4, 50 °C. (b) (1) BnBr, (2) 50 °C, 67%. (c) $LiAlH_4/Et_2O$, 93%. (d) (1) HCl, 6N, (2) H_2, Pd/C, 95%.

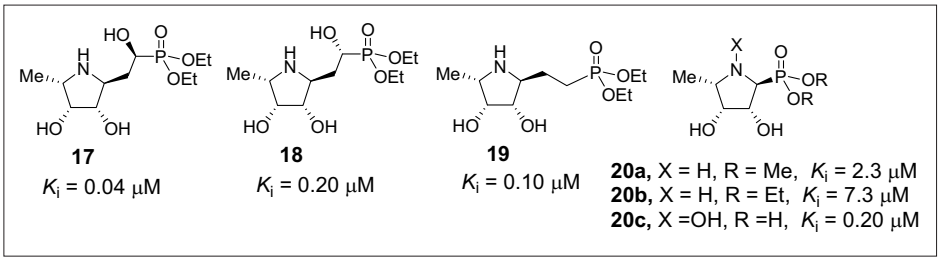
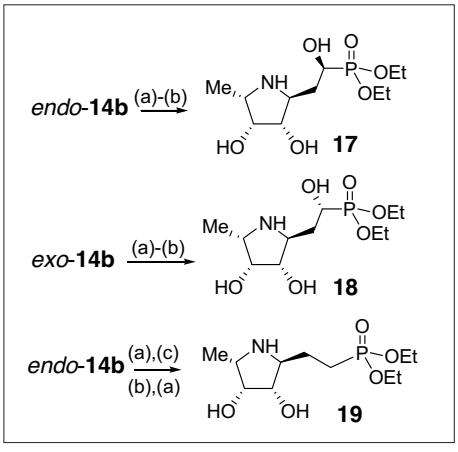


Fig. 3. Inhibitory activities of **17**–**20** towards α-L-fucosidases from bovine kidney.



Scheme 7. Reagents and conditions: (a) H_2, Pd/C, EtOH, 40 °C. (b) HCl, 6 N. (c) (1) $ClCO_2Bn$, $NaHCO_3$, (2) Im_2CS, THF. (3) Bu_3SnH, AIBN.

Phosphonate derivatives **17**–**20** showed inhibitory activities in the sub-micromolar to nanomolar range (Fig. 3).[21a,26]

Compounds **17**–**19** were also obtained from nitrone **8** by reaction with vinylphosphonate **13b** as indicated in Scheme 4. Ring opening of *endo*-**14b** followed by deprotection gave the corresponding diol **17** (Scheme 7).[21a] The same procedure applied to phosphonate *exo*-**14b** gave compound **18**. Ring opening of *endo*-**14b** followed by β-elimination and deprotection afforded phosphonate **19**.[21a] On the other hand, addition of alkyl phosphates to nitrone **8** followed by deprotection afforded pyrrolidinephosphonates **20a**–**c**.[26]

Pyrrolidine-3,4-diol derivatives sharing the absolute configuration at C(2,3,4,5) of L-fucopyranosides and incorporating aromatic moieties at C(2) have been shown to be competitive, potent and selective inhibitors of α-L-fucosidases. Thus, 1,4-imino-*C*-benzimidazole **21a**, phenyl (and biphenyl) aminomethyl pyrrolidines (**22a** and **22b**) present inhibition constants in the nanomolar range.[27] Additionally, compound **21b**[27c] which bears a hydroxyethyl group at C(5) on the pyrrolidine moiety and L-*fuco* configuration on C(2,3,4,5) shows a decrease in the inhibitory properties, in accordance with the described small hydrophobic pocket in the active site of α-L-fucosidases (Fig. 4).[23] Compound **23**,[27a,c] epimer at C(5) of **21a**, proved to be a weaker inhibitor (K_i = 240 μM) of α-L-fucosidase from bovine kidney but a good inhibitor (K_i = 46 μM) of β-glucosidase from almonds.

The synthesis of compounds **21a** and **22a**,**b** was carried out through the stereoselective preparation of carbaldehyde **24** as key intermediate. Oxidation to the corresponding pyrrolidine carboxylic acid, reaction with *o*-phenylenediamine in the presence of PyBOP and DIEA and subsequent heating in acetic acid and deprotection easily gave **21a** bearing a benzymidazole moiety at C(2). The synthesis of aminomethyl pyrrolidines **22a** and **22b** was carried out starting from aldehyde **24** by reductive amination with aniline and biphenyl-4-amine respectively followed by deprotection (Scheme 8).[27a,c]

Other derivatives with hydroxylic substituents, several alkyl substituents at C(5) and different configurations at C(2) and C(5) of the pyrrolidine ring (compounds **25**–**30**) were also reported, showing to be also inhibitors of α-L-fucosidases (Fig. 5).[23,25,28,29]

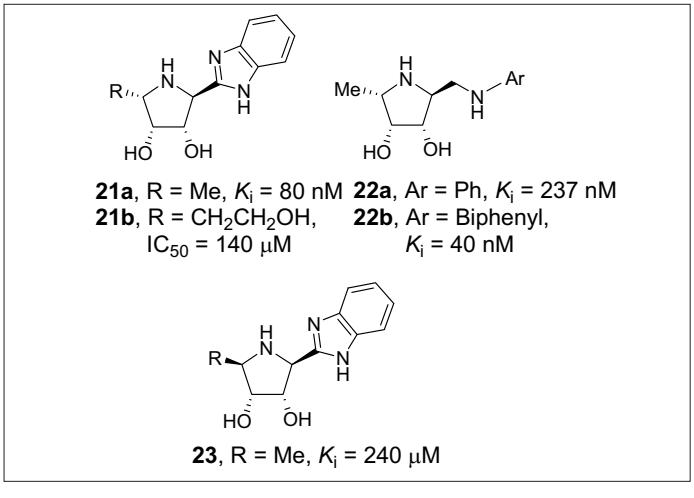
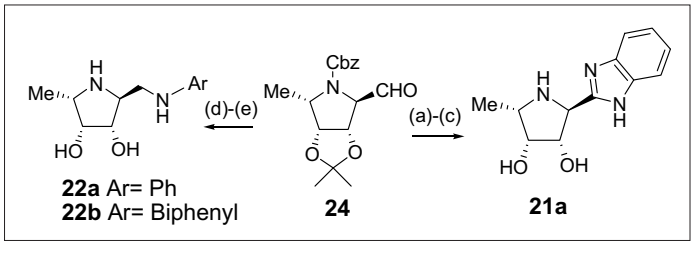


Fig. 4. Inhibitory activities of **21**–**23** towards α-L-fucosidases from bovine kidney.



Scheme 8. Reagents and conditions: (a) $NaClO_2$, KH_2PO_4, *t*-BuOH-H_2O. (b) (1) *o*-phenylenediamine, PyBOP, DIEA, DMF, 65%, (2) AcOH, 50 °C, 100%. (c) (1) THF:HCl (1N) 1:1, (2) H_2, Pd/C, MeOH, 87% (1+2). (d) $ArNH_2$, $NaBH(AcO)_3$, 66–75%. (e) (1) HCl (1N), (2) H_2, Pd/C, MeOH, quant.

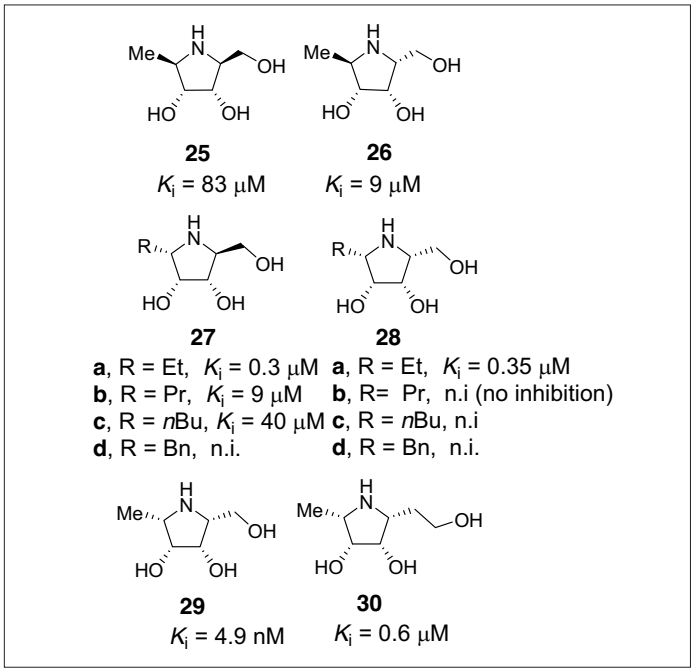
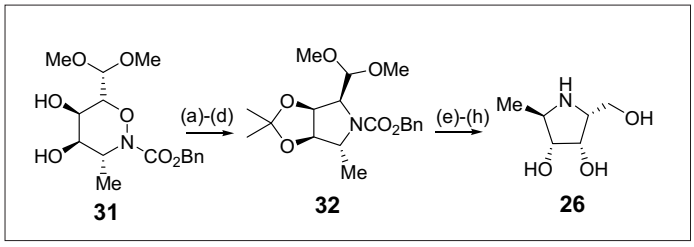
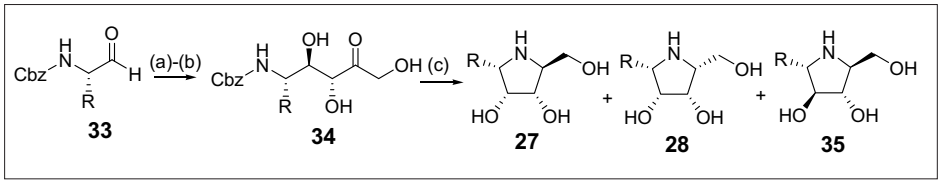


Fig. 5. Inhibitory activities of **25**–**30** towards α-L-fucosidases from bovine kidney.



Scheme 9. Reagents and conditions: (a) (1) 2,2-Dimethoxypropane/ Amberlyst 15 (H^+), quant., (2) H_2/Pd-C. (b) $ClCO_2Bn$/NaOH, 84%. (c) $ClSO_2Me/NEt_3$. (d) 1N NaOH/MeOH. (e) Amberlyst 15 (H^+)/acetone, 80%. (f) $NaBH_4$/MeOH. (g) Amberlyst 15 (H^+)/EtOH. (h) H_2/Pd-C.



Scheme 10. Reagents and conditions: (a) Fuc aldolase. (b) acid phosphatase. (c) H_2 (50 psi), Pd/C. **27**:**28**:**35**, **a**, R = Et, 86:4:10; **b**, R = Pr, 86:10:4; **c**, R = Bu, 80:10:10; **d**, R = Bn, 62:38:0.

The synthesis of compound **25** was carried out by Jäger and coworkers.[28a] The synthetic sequence is based on the transformation of a 3,4-isopropylidenedioxy-5-methylpyrrolidine-1-oxide with a 2-methyl substituent into the free diol and, by reduction, into the corresponding pyrrolidine diol. The pyrrolidine *N*-oxide was derived from D-ribose *via* an unsaturated hydroxylamine, with the key steps of nitrone addition and Cope-House cyclization. The synthesis of compound **25** was also reported by Defoin and coworkers through an asymmetric hetero-Diels-Alder cycloaddition, starting from sorbaldehyde dimethylacetal in 13 steps and an overall yield of 9.5%.[30] The synthesis of **26** was carried out through an asymmetric hetero-Diels-Alder cycloaddition of sorbaldehyde dimethylacetal with an α-chloronitroso derivative as key step.[31] Subsequent chemical modifications gave the intermediate oxazane-diol **31** which after several transformations afforded trihydroxypyrrolidine **26** (Scheme 9).[30b]

Compounds **27** and **28** were prepared by Clapés and coworkers[23] through a chemo-enzymatic synthesis as depicted in Scheme 10. In these iminocyclitols, the configuration at positions C(3) and C(4) was controlled by the DHAP aldolase, the configuration of C(5) was fixed by the starting aldehyde and the stereogenic center at C(2) was generated during the reductive amination and depended, in most cases, on the configuration of C(4).

Compounds **27a** and **28a** were found to be potent inhibitors of α-L-fucosidases from bovine kidney (K_i = 0.35 μM) whereas **35a** (IC_{50} = 100 μM) was much less active. The related compounds **6** (Fig. 2) and **29** (Fig. 5), analogues of **27a** and **28a**, respectively, which carry a 5-methyl substituent instead of the ethyl group, were found to be more potent α-L-fucosidase inhibitors with K_i = 80 and 4.9 nM, respectively. Increasing the length of the substituent at C(5) from methyl (*e.g.* **6** and **29**) to ethyl (*e.g.* **27a** and **28a**), propyl (*e.g.* **27b**), or butyl (*e.g.* **27c**) implied a progressive loss of inhibitory activity. Compounds **27d**, **28b–d** showed a complete loss of activity, which is in accordance with a relatively small hydrophobic pocket in the active site of the enzyme. In this respect, Behr and coworkers described that the substitution of the Me group at C(5) by a spirocyclopropyl moiety such as compound **36** (K_i = 1.6 μM), led to a decrease on the bovine kidney α-L-fucosidase inhibition compared to the pyrrolidine analogue **37** (K_i = 0.2 μM) (Fig. 6).[32]

Spirocyclopropyl iminosugar **36** was prepared in four steps from readily available D-mannose diacetonide. The key step of the reaction sequence involves a titanium-mediated aminocyclopropanation of a glycononitrile with subsequent cyclization.[32]

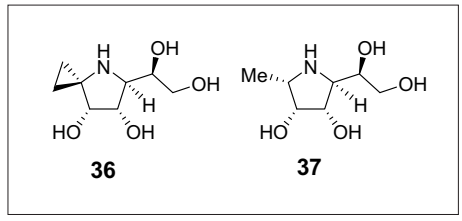


Fig. 6.

Other derivatives that do not share the L-*fuco* configuration and that bear aromatic substituents such as in **38** and **39** have been described as α-L-fucosidase from bovine kidney inhibitors but are weaker inhibitors than compound **21a** (Fig. 7).[27c]

Compounds **38** and **39** were prepared from pyrrolidine-esters **41** and **44** as key intermediates, respectively (Scheme 11). The preparation of **41** and **44** started from D-ribose and L-fucose through conjugate addition of ammonia-internal S_N2 displacement to conjugated aldonic esters as the key step.

3. Conclusions

Several 1,4-iminoalditol derivatives have proved to be effective α-L-fucosidase inhibitors. They constitute an important class of iminosugars with promising biological and therapeutic properties. Although several strategies have been developed to synthesize these compounds, much remains to be done in order to find effective and selective α-L-fucosidase inhibitors.

Acknowledgements

We thank the Ministerio de Ciencia e Innovación of Spain (CTQ2008-01565/BQU) and the Junta de Andalucía (FQM 345) for financial support. E.M.-C. thanks the Ministerio de Educación for a FPU fellowship.

Received: July 13, 2010

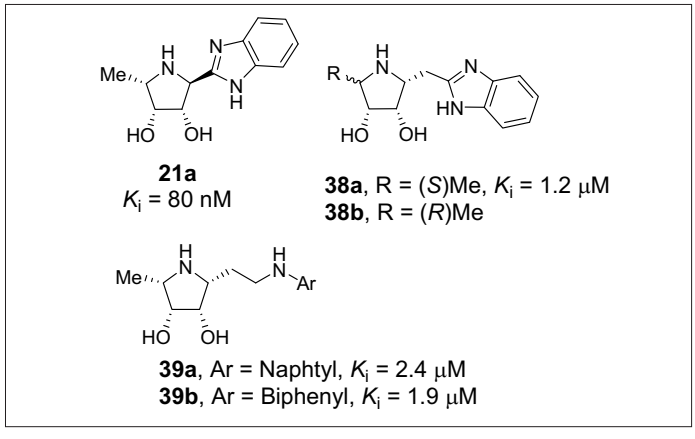
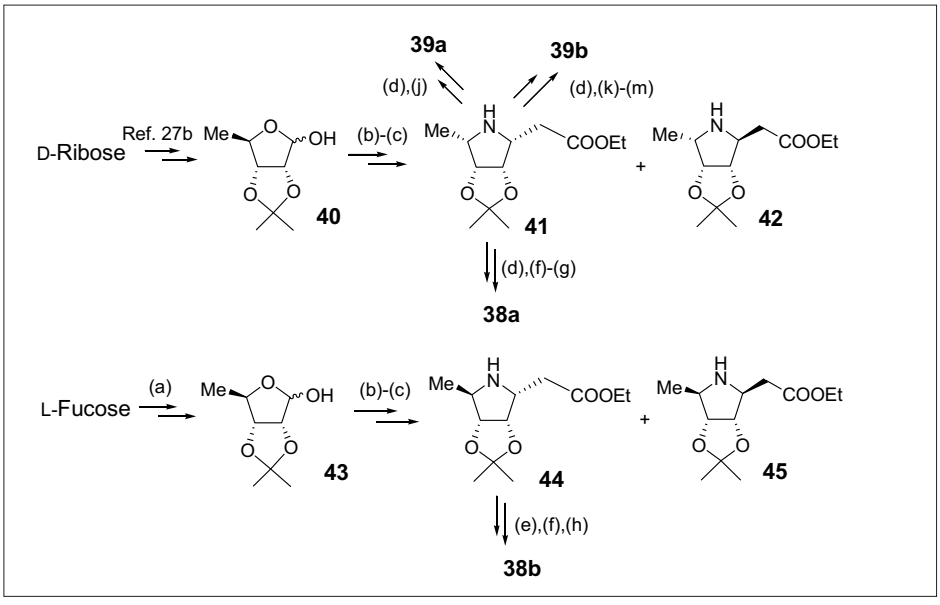


Fig. 7. Inhibitory activities of **21a**, **38**, **39** towards α-L-fucosidases from bovine kidney.



Scheme 11. Reagents and conditions: (a) (1) 2,2-DMP, PTSA, (2) $NaIO_4$, H_2O, (3) NaOH, (4) HCl, 65% (overall). (b) $Ph_3P{=}CH_2COOEt$, CH_2Cl_2 reflux, 90% from **40**, 70% (in toluene reflux) from **43**. (c) (1) MsCl, Py, (2) NH_3, EtOH, 50–76%. (d) Boc_2O, Py, 92%. (e) CbzCl, EtOH, $NaHCO_3$, 90% (f) (1) NaOH, EtOH, (2) *o*-phenylenediamine, PyBOP, DIEA, DMF, (3) AcOH, 50 °C, 76%. (g) (1) HCl, (2) NH_4OH, 64%. (h) (1) H_2, Pd/C, MeOH, (2) HCl, THF, 58%. (j) (1) DIBALH, CH_2Cl_2, -78 °C, (2) $ArNH_2$, $NaBH(AcO)_3$, (3) HCl (1N), THF, (4) NH_4OH, 40% (overall for **39a**). (k) (1) NaOH, EtOH, (2) Ar-NH_2, PyBOP, DIEA, DMF. (l) BH_3, Me_2S, THF. (m) (1) HCl 1N, THF, (2) NH_4OH, 86% (overall for **39b**).

[1] a) A. Giannis, *Angew. Chem. Int. Ed.* **1994**, *33*, 178; b) H. M. Flowers, *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 279; c) T. K. Lindhorst, M. Ludewig, J. Thiem, *J. Carbohydr. Chem.* **1998**, *17*, 1131.

[2] a) B. Cobucci-Ponzano, M. Mazzone, M. Rössi, M. Moracci, *Biochemistry* **2005**, *44*, 6331; b) P. T. Vanhooren, E. J. Vandamme, *J. Chem. Technol. Biotechnol.* **1999**, *74*, 479; c) E. Staudacher, F. Altmann, I. B. Wilson, L. Marz, *Biochim. Biophys. Acta* **1999**, *1473*, 216; d) L. A. Lasky, *Annu. Rev. Biochem.* **1995**, *63*, 113; e) M. S. Mulligan, J. C. Paulson, S. DeFrees, Z. L. Zheng, J. B. Lowe, P. A. Ward, *Nature* **1993**, *364*, 149; f) F. Schweizer, *Angew. Chem. Int. Ed.* **2002**, *41*, 230.

[3] G. Osanjo, M. Dion, J. Drone, C. Solleux, V. Tran, C. Rabiller, C. Tellier, *Biochemistry* **2007**, *46*, 1022.

[4] J. C. Michalski, A. Klein, *Biochim. Biophys. Acta* **1999**, *1455*, 69.

[5] a) P. Compain, O. R. Martin, *Bioorg. Med. Chem.* **2001**, *9*, 3077; b) T. A. Springer, L. A. Lasky, *Nature* **1991**, *349*, 196; c) J. B. Lowe, *Inmunol. Rev.* **2002**, *186*, 19.

[6] a) M. C. Glick, V. A. Kothari, A. Liu, L. I. Stoykova, T. F. Scanlin, *Biochimie* **2001**, *83*, 743; b) T. F. Scanlin, M. C. Glick, *Biochim. Biophys. Acta* **1999**, *1455*, 241.

[7] a) D. Ayude, J. Fernández-Rodríguez, F. J. Rodríguez-Berrocal, V. S. Martínez-Zorzano, A. de Carlos, E. Gil, M. P. de la Cadena, *Oncology* **2000**, *59*, 310; b) J. Fernández-Rodríguez, D. Ayude, M. P. de la Cadena, V. S. Martínez-Zorzano, A. de Carlos, A. Caride Castro, G. de Castro, F. J. Rodríguez-Berrocal, *Cancer Detect. Prev.* **2000**, *24*, 143.

[8] W. L. Hutchinson, P. J. Johnson, M. Q. Du, R. Williams, *Clin. Sci.* **1991**, *81*, 177.

[9] a) S. Khunnsook, B. Bean, S. R. McGowan, J. A. Alhadeff, *Biol. Reprod.* **2003**, *68*, 709; b) S. Khunnsook, J. A. Alhadeff, B. Bean, *Mol. Hum. Reprod.* **2002**, *8*, 221.

[10] C. Rosano, S. Zuccotti, B. Cobucci-Ponzano, M. Mazzone, M. Rossi, M. Moracci, M. V. Petoukhov, D. I. Svergun, M. Bolognesi, *Biochem. Biophys. Res. Commun.* **2004**, *320*, 176.

[11] A. Lammerts van Bueren, Ardévol, J. Fayers-Kerr, B. Luo, Y. Zhang, M. Sollogoub, Y. Blériot, C. Rovira, G. J. Davies, *J. Am. Chem. Soc.* **2010**, *132*, 1804.

[12] G. Sulzenbacher, C. Bignon, T. Nishimura, C. A. Tarling, S. G. Withers, B. Henrissat, Y. Bourne, *J. Biol. Chem.* **2004**, *279*, 13119.

[13] M. Nagae, A. Tsuchiya, T. Katayama, K. Yamamoto, S. Wakatsuki, R. Kato, *J. Biol. Chem.* **2007**, *282*, 18497.

[14] H.-J. Wu, C.-W. Ho, T.-P. Ko, S. D. Popat, C.-H. Lin, A. H.-J. Wang, *Angew. Chem. Int. Ed.* **2010**, *49*, 337.

[15] I. Robina, A. J. Moreno-Vargas, A. T. Carmona, P. Vogel, *Curr. Drug. Metabol.* **2004**, *5*, 329.

[16] J. Guo, J. Asong, G.-J. Bons, *Angew. Chem. Int. Ed.* **2006**, *45*, 5345.

[17] B. A. Johns, Y. T. Pan, A. D. Elbein, C. R. Johnson, *J. Am. Chem. Soc.* **1997**, *119*, 4856.

[18] a) C. Legler, *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319; b) S. J. Charnock, T. D. Spurway, H. Xie, M.-H. Beylot, R. Virden, R. A. J. Warren, G. P. Hazlewood, H. J. Gilbert, *J. Biol. Chem.* **1998**, *273*, 32187; c) M. Bols, V. H. Lillelund, H. H. Jensen, X. Liang, *Chem. Rev.* **2000**, *102*, 515.

[19] a) F. Popowycz, S. Gerber-Lemaire, R. Demange, E. Rodríguez-García, A. T. Carmona Asenjo, I. Robina, P. Vogel, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2489; b) A. T. Carmona, F. Popowycz, S. Gerber-Lemaire, E. Rodríguez-García, C. Schütz, P. Vogel, I. Robina, *Bioorg. Med. Chem.* **2003**, *11*, 4897.

[20] a) I. Robina, A. J. Moreno-Vargas, J. G. Fernández-Bolaños, J. Fuentes, R. Demange, P. Vogel, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2555; b) A. J. Moreno-Vargas, R. Demange, J. Fuentes, I. Robina, P. Vogel, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2335; c) A. J. Moreno-Vargas, I. Robina, R. Demange, P. Vogel, *Helv. Chim. Acta* **2003**, *86*, 1894.

[21] a) C. Chevrier, D. Le Nouën, M. Neuburger, A. Defoin, C. Tarnus, *Tetrahedron Lett.* **2004**, *45*, 5363; b) A. Defoin, C. Tarnus, J. Streith, *Synlett* **2000**, 1366.

[22] C.-H. Wong, L. Provencher, J. A. Jr. Porco, S.-H. Jung, Y.-F. Wang, L. Chen, R. Wang, D. H. Steensma, *J. Org. Chem.* **1995**, *60*, 1492.

[23] J. Calveras, M. Egido-Gabás, L. Gómez, J. Casas, T. Parella, J. Joglar, J. Bujons, P. Clapés, *Chem. Eur. J.* **2009**, *15*, 7310.

[24] V. Jäger, L. Bierer, H.-Q. Dong, A. M. Palmer, D. Shaw, W. Frey, *J. Heterocyclic. Chem.* **2000**, *37*, 455.

[25] Y. F. Wang, D. P. Dumas, C.-H. Wong, *Tetrahedron Lett.* **1993**, *34*, 403.

[26] C. Chevrier, D. Le Nouën, A. Defoin, C. Tarnus, *Eur. J. Org. Chem.* **2006**, 2384.

[27] a) A. J. Moreno-Vargas, A. T. Carmona, F. Mora, P. Vogel, I. Robina, *Chem. Commun.* **2005**, 4949. b) E. Moreno-Clavijo, A. T. Carmona, A. J. Moreno-Vargas, I. Robina, *Tetrahedron Lett.* **2007**, *48*, 159; c) E. Moreno-Clavijo, A. T. Carmona, Y. Vera-Ayoso, A. J. Moreno-Vargas, C. Bello, P. Vogel, I. Robina, *Org. Biomol. Chem.* **2009**, *7*, 1192.

[28] a) A. M. Palmer, V. Jäger, *Eur. J. Org. Chem.* **2001**, 2547; b) T. Sifferlen, A. Defoin, J. Streith, D. LeNouen, C. Tarnus, I. Dosbaa, M.-J. Foglietti, *Tetrahedron* **2000**, *56*, 971; c) A. M. Palmer, V. Jäger, *Eur. J. Org. Chem.* **2001**, 1293.

[29] E. Moreno-Clavijo, Ph.D. Thesis, University of Seville, **2010**.

[30] a) A. Defoin, Th. Sifferlen, J. Streith, I. Dosbaâ, M.-J. Foglietti, *Tetrahedron: Asymm.* **1997**, *8*, 363; b) T. Sifferlen, A. Defoin, J. Streith, D. Le Nouën, C. Tarnus, I. Dosbaâ, M.-J. Foglietti, *Tetrahedron* **2000**, *56*, 971.

[31] a) A. Defoin, H. Sarazin, J. Streith, *Tetrahedron* **1997**, *53*, 13769; b) A. Defoin, H. Sarazin, J. Streith, *Tetrahedron* **1997**, *53*, 13783.

[32] a) C. Laroche, J. B. Behr, J. Szymoniak, P. Bertus, C. Schütz, P. Vogel, R. Plantier-Royon, *Bioorg. Med. Chem.* **2006**, *14*, 4047; b) J.-B. Behr, M. S. M. Pearson, C. Bello, P. Vogel, R. Plantier-Royo, *Tetrahedron: Asymm.* **2008**, *19*, 1829.