Synthesis and biological evaluation of α-1-*C*-4'-arylbutyl-L-arabinoiminofuranoses, a new class of α-glucosidase inhibitors

Yoshihiro Natori, Toshihiro Sakuma, Yuichi Yoshimura, Kyoko Kinami, Yuki Hirokami, Kasumi Sato, Isao Adachi, Atsushi Kato, Hiroki Takahata

PII: S0960-894X(14)00613-1
DOI: http://dx.doi.org/10.1016/j.bmcl.2014.06.001
Reference: BMCL 21718

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 19 May 2014
Revised Date: 29 May 2014
Accepted Date: 2 June 2014

Please cite this article as: Natori, Y., Sakuma, T., Yoshimura, Y., Kinami, K., Hirokami, Y., Sato, K., Adachi, I., Kato, A., Takahata, H., Synthesis and biological evaluation of α-1-*C*-4'-arylbutyl-L-arabinoiminofuranoses, a new class of α-glucosidase inhibitors, *Bioorganic & Medicinal Chemistry Letters* (2014), doi: http://dx.doi.org/10.1016/j.bmcl.2014.06.001

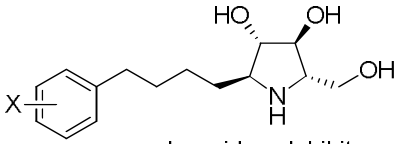
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthesis and biological evaluation of α-1-*C*-4'-arylbutyl-L-arabinoiminofuranoses, a new class of α-glucosidase inhibitors

Leave this area blank for abstract info.

Yoshihiro Natori[a], Toshihiro Sakuma[a], Yuichi Yoshimura[a,*], Kyoko Kinami[b], Yuki Hirokami[b], Kasumi Sato[b], Isao Adachi[b], Atsushi Kato[b,*], Hiroki Takahata[a,§]



α-glucosidase Inhibitors

up to 163-fold stronger than miglitol
(X = 3,5-diF)

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Synthesis and biological evaluation of α-1-*C*-4'-arylbutyl-L-arabinoiminofuranoses, a new class of α-glucosidase inhibitors

Yoshihiro Natori[a], Toshihiro Sakuma[a], Yuichi Yoshimura[a,*], Kyoko Kinami[b], Yuki Hirokami[b], Kasumi Sato[b], Isao Adachi[b], Atsushi Kato[b,*], Hiroki Takahata[a,§]

[a]*Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, Sendai 981-8558, Japan*
[b]*Department of Hospital Pharmacy, University of Toyama, Toyama 930-0194, Japan*
[§]Deceased on 1st March, 2014

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords
Iminosugars
1-*C*-4'-Arylbutyl-L-arabinoiminofuranoses
α-Glucosidase inhibitor
Type-2 diabetes
Structure-activity relationship

ABSTRACT

A series of α-1-*C*-4'-arylbutyl-L-arabinoiminofuranoses **3** with functional groups attached to the phenyl ring, which are potential α-glycosidase inhibitors, was designed and synthesized by using a Negishi cross-coupling reaction as the key reaction. Arylbutyl derivatives **3a–e** showed potent inhibitory activities against intestinal maltase. Among them, difluorophenylbutyl derivative **3e** showed good inhibition activities against intestinal isomaltase and sucrase as compared to those of **1** and commercial drugs.©

Iminosugars are sugar mimics with nitrogen atoms instead oxygen atoms in the monosaccharides, and they inhibit various glycosidases in a reversible and competitive manner. These inhibitors are currently of great interest as potential therapeutic agents.[1] α-Glucosidase inhibitors are used in the treatment of type-2 diabetes because they delay the absorption of carbohydrates, which allows beta cells to increase insulin secretion, thus reducing the glucose levels during circulation and especially during the postprandial period. On the basis of the benefits of α-glucosidase inhibitors, three drugs for the treatment of type-2 diabetes, acarbose (Glucobay™), voglibose (Basen™), and miglitol (Glyset™), have been approved for use and are currently on the market.[2,3] However, the carbasugar-based drugs, such as acarbose and voglibose, have been associated with a high frequency of side effects, such as flatulence, diarrhea, and hypoglycemia, because the drugs stay in the intestine and colon for long periods of time.[4] In the worst case, it has been reported that they cause fulminant hepatitis.[5] In contrast, the iminosugar-based drug miglitol has been designed to be absorbed almost completely from the intestinal tract. However, it may cause systemic effects in addition to affecting the intestinal border.[6] Moreover, an absorbable inhibitor, such as miglitol, may exert an inhibitory effect on nonintestinal α-glucosidases present in the various cell types of the body as a side-effect.[7] Therefore, our strategy has been to design effective iminosugar-type α-glucosidase inhibitors that affect postprandial hyperglycemia while showing strong inhibitory effects against maltase, isomaltase, and sucrase and that do not interfere with the processing of glycoproteins. As part of our research program aimed at developing new potent and selective α-glucosidase inhibitors ,[8] we have recently reported the synthesis and biological evaluation of a series of α-1-*C*-alkylated 1,4-dideoxy-1,4-imino-L-arabinitol (LAB) derivatives as a new class of promising compounds that can be used to treat postprandial hyperglycemia.[9] Among them, α-1-*C*-butyl-LAB **1** strongly suppresses postprandial hyperglycemia during early stages, similar to miglitol *in vivo*, with an effective dose about 10-fold lower than that for miglitol. In addition, α-1-*C*-4'-phenybutyl-L-arabinoiminofuranose **2** shows inhibitory activities against intestinal maltase and isomaltase similar to those of **1**, although the inhibitory potency of **2** against intestinal sucrase is lower than that of **1**.[9a] Therefore, we focused on the effects of the substituents on the phenyl ring of **2** on the inhibitory activities against α-glucosidases.

Herein we report the synthesis of α-1-*C*-4'-arylbutyl-L-arabinoiminofuranoses **3** with different functional groups attached to the phenyl ring and their inhibitory activities against intestinal α-glucosidases.

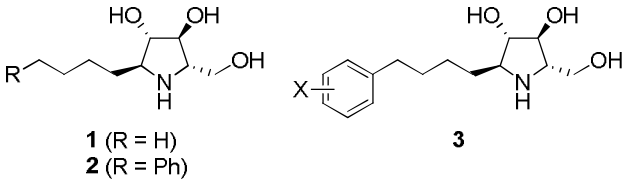
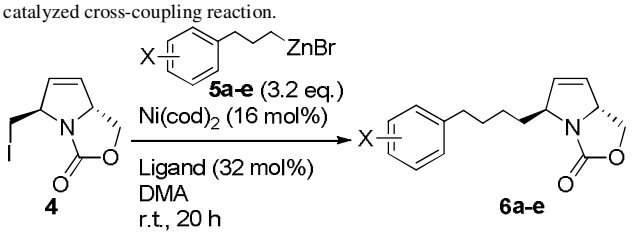


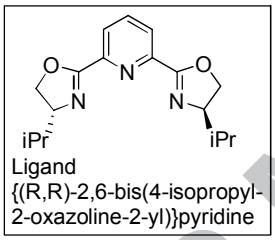
Figure 1. Structures of 1-substituted L-arabinoiminofuranoses**.**

An iodomethyl derivative **4** was prepared by using a modified Trost procedure[10] with asymmetric allylic alkylation (AAA) and ring closing metathesis (RCM) as the key reactions, as reported previously.[9] A Csp^3–Csp^3 bond formation reaction using a nickel-catalyzed Negishi cross-coupling reaction[11] of **4** with 3-arylpropylzinc bromides **5a–e** gave 4-arylbutylated bicyclic 2,5-dihydropyrroles **6a–e** in good yields (Scheme 1 and Table 1).

Scheme 1 and Table 1. Csp^3–Csp^3 bond formation reactions using a nickel-catalyzed cross-coupling reaction.



entry	X	yield (%)[a]
1	4-Me (**5a**)	81
2	4-MeO (**5b**)	65
3	4-AcO(**5c**)	64
4	4-F (**5d**)	79
5	3,5-diF (**5e**)	80



[a] Isolated yield.
(DMA = *N*,*N*-dimethylacetamide)

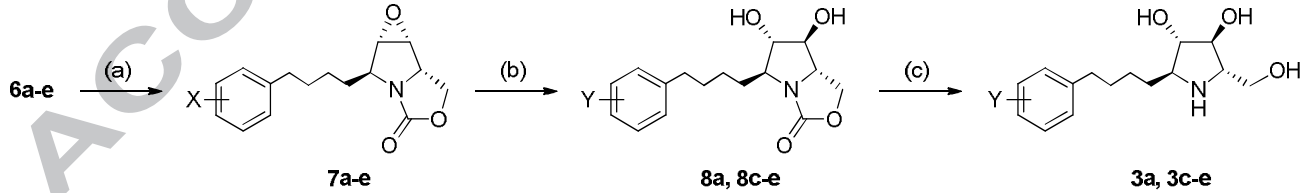
The epoxidation of the olefin moiety in **6a–e** with dioxirane, which was generated *in situ* from the reaction of Oxone™ with 1,1,1-trifluoroacetone, stereoselectively afforded epoxides **7a,c–e**, whereas **7b** was not detected because the reaction involving **6b** resulted in the oxidation of the anisyl ring to give a complex mixture. Ring-opening of the epoxide moieties in **7a,c–e** with aqueous trifluoroacetic acid stereoselectively proceeded to afford diols **8a,d,e**.[9,10] Under the conditions used, in the case of **7c**, hydrolysis of the acetate group occurred, affording phenol **8c**. Finally, oxazolinones **8a,c–e** were transformed into the desired iminosugars **3a,c–e** by using basic hydrolysis (Scheme 2 and Table 2).

In addition, iminosugar **3b** was obtained by methylation of **8c** with trimethylsilyldiazomethane, followed by treatment with NaOH, in two-steps in 41% yield (Scheme 3).

Next the abilities of **3a–e** to act as inhibitors against intestinal α-glucosidases (maltase, isomaltase, and sucrase) were examined[12] since they could be of value in managing type-2 diabetes, as demonstrated by similar commercially available drugs (acarbose (Glucobay™), voglibose (Basen™), and miglitol (Glyset™)). The results are summarized in Table 3.

We have previously reported that α-1-*C*-butyl-LAB **1** is an excellent inhibitor against intestinal maltase, isomaltase, and sucrase with IC_{50} values of 0.13, 4.7, and 0.032 μM, respectively.[9(a)] On the basis of these finding, we first investigated whether or not adding a phenyl group to the 1-*C*-butyl terminal position affected the inhibition activities of **1**. However, as shown in Table 3, the phenyl substituent did not enhance intestinal maltase inhibition (**2**: IC_{50} = 0.22 μM). For comparison, we investigated whether the introduction of substituents on the phenyl ring had an effect on the inhibition of these enzymes. The inhibition potencies of compounds **3a–e** against maltase were similar to that of **1** (IC_{50} = 0.11–0.34 μM). Thus, it was concluded that electronic factors did not affect the inhibition against maltase. On the other hand, **3a** and **3e** showed much better inhibition against isomaltase than that of **1** with IC_{50} values of 0.63 and 0.22 μM, respectively. In addition, both **3a** and **3e** showed excellent inhibitory activities against sucrase (IC_{50} = 0.045 and 0.026 μM, respectively), which are comparable to that of **1** (IC_{50} = 0.032 μM). In contrast, **3b–d** and **2** are 3–10-fold weaker sucrase inhibitors than **1** is. Moreover, no significant electronic effects of the substituents were observed.

However, there was a striking difference between **3d** and **3e** with fluoro substituents, which are strong withdrawing groups, toward the inhibitions of isomaltase and sucrase. Namely, difluoro **3e** was found to be a much stronger inhibitor against both isomaltase and sucrase than monofluoro derivative **3d** was, whereas a slight reduction in the inhibitory activities of **3e** against maltase was observed. In addition, **3a** and **3e** were found to be 62-fold and 163-fold stronger inhibitors, respectively, against every α-glucosidases than miglitol was. Moreover, **3a** and

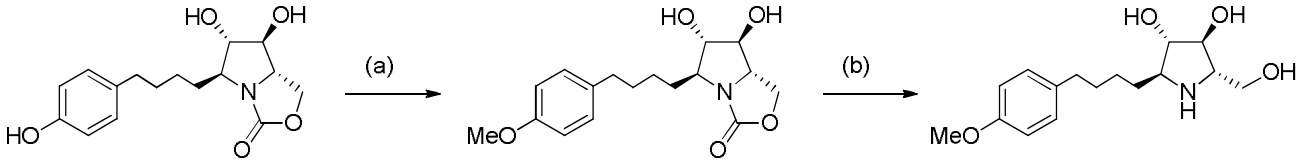


Scheme 2. Reagents and conditions: (a) CF_3COCH_3, Oxone™, $NaHCO_3$, CH_3CN-aq. Na_2EDTA (3:2), 0 °C (b) CF_3CO_2H, THF-H_2O (3:2), 80 °C (c) NaOH, EtOH-H_2O (2:1), 100 °C.

Table 2. Summary of syntheses of **3** from **6**

	procedure (a) (**6** → **7**)		procedure (b) (**7** → **8**)		procedure (c) (**8** → **3**)	
entry	X	yield (%)[a]	Y	yield (%)[a]	Y	yield (%)[a]
1	4-Me (**7a**)	90	4-Me (**8a**)	77	4-Me (**3a**)	58
2	4-MeO (**7b**)	not detected				
3	4-AcO(**7c**)	99	4-HO(**8c**)	76	4-HO(**3c**)	61
4	4-F (**7d**)	88	4-F (**8d**)	96	4-F (**3d**)	53
5	3,5-diF (**7e**)	92	3,5-diF (**8e**)	90	3,5-diF (**3e**)	63

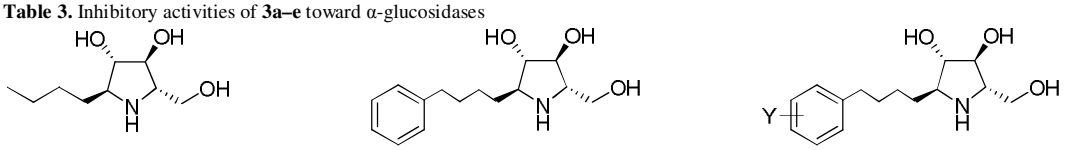
[a] Isolated yield.



8c **8b** **3b**

Scheme 3. Reagents and conditions: (a) $TMSCHN_2$ (2.0 M in Et_2O) CH_2Cl_2-MeOH (2:1), 0 °C (b) NaOH, EtOH-H_2O (2:1), 100 °C.

Table 3. Inhibitory activities of **3a–e** toward α-glucosidases



α-1-*C*-butyl-LAB (**1**) α-1-*C*-(4-phenyl)butyl-LAB (**2**) **3a-e**

	IC_{50} (μM)		
Compounds	Maltase	Isomaltase	Sucrase
α-1-*C*-butyl-LAB (**1**)	0.13	4.7	0.032
α-1-*C*-(4-phenyl)butyl-LAB (**2**)	0.22	14	0.31
3a (Y = 4-Me)	0.28	0.63	0.045
3b (Y = 4-MeO)	0.11	1.8	0.13
3c (Y = 4-HO)	0.17	6.0	0.11
3d (Y = 4-F)	0.18	3.0	0.17
3e (Y = 3,5-diF)	0.34	0.22	0.026
acarbose	0.18	NI	2.9
voglibose	0.12	5.2	0.37
miglitol	1.3	39	1.0

NI: less than 50% inhibition at 1000 μM

3e and **1** showed comparable inhibitory activities against maltase and sucrase. In sharp contrast, **3a** and **3e** are 7-fold and 21-fold greater inhibitors, respectively, against isomaltase than **1** is. We found that changing the butyl and 4-phenyl groups to a 4-(4-methylphenyl)butyl or a 4-(3,5-difluorophenyl)butyl group resulted in a greater specificity for inhibiting isomaltase. In other words, we observed that the substituent on the phenyl ring of **2** dramatically affected the inhibition abilities against certain α-glucosidases. Since intestinal absorption of dietary disaccharides is mediated by a group of α-glucosidases, which include intestinal maltase, isomaltase, and sucrase, inhibition of these enzymes can significantly decrease postprandial hyperglycemia.[9(a),12] Among these intestinal α-glucosidases, isomaltase cleaves the α-1-6 bonds linking the saccharides, which cannot be broken by amylase or maltase. This study revealed that, of the prepared α-1-*C*-4'-arylbutyl-L-arabinoiminofuranoses, **3e** was the most potent and selective inhibitor against intestinal isomaltase. In addition, **3e** is 4500-fold and 570-fold more potent against isomaltase than acarbose and miglitol, respectively, are. In other words, **3e** will be an excellent α-glucosidase inhibitor for treating postprandial hyperglycemia.

In summary, we synthesized a series of α-1-*C*-4'-arylbutyl-L-arabinoiminofuranoses with functional groups on the phenyl ring (**3**) for use as AGIs by using a Negishi cross-coupling reaction as the key reaction. The inhibitory activities of arylbutyl derivatives **3a–e** against intestinal maltase were comparable to that of the original butyl derivative **1**. Among them, difluorophenylbutyl derivative **3e** showed a greater inhibitory activity against intestinal isomaltase than **1** and commercial drugs did. In addition, the inhibitory potency of **3e** (IC_{50} = 0.026 μM) against intestinal sucrase was the same as that of **1** (IC_{50} = 0.032 μM). We are currently studying the effects of a wide variety of substituents on the phenyl ring of **3** on their inhibition activities.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Young Scientists (B) (No. 23790138) (Y.N.) from JSPS and by a Grant of Strategic Research Foundation Grant-aided Project for Private Universities from Ministry of Education, Culture, Sport, Science, and Technology, Japan (MEXT), 2010–2014.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://@@

References and notes

1. (a) Compain, P.; Martin, O. R. Iminosugars—From Synthesis to Therapeutic Applications; John Wiley & Sons Ltd.: West Sussex, England, 2007. (b) Asano, N.; Oseki, K.; Tomioka, E.; Kizu, H.; Matsui, K. *Carbohydr. Res*. **1994**, *259*, 243.
2. Nash, R. J.; Kato, A.; Yu, C.-Y.; Fleet, G. W. J. *Future, Med. Chem.* **2011**, *3*, 1513.
3. Horne, G.; Wilson, F. X. *Prog, in Med. Chem.* **2011**, *50*, 135.
4. (a) Putter, J. In *Enzyme Inhibitors*, Brodech, E., Ed.; Verlag Chemie: Weinheim, Germany, 1980; p139. (b) Holmn, R. R.; Cull, C. A.; Turner, R. C. *Diabetes Care*., **1999**, *22*, 960.
5. Carrascosa, M.; Pascual, F.; Aresti, S. *Lancet* **1997**, *349*, 698.
6. (a) Joubert, P. H.; Venter, H. L.; Foukaridis, G. N. *Br. J. Clin. Pharmacol*. **1990**, *30*, 391. (b) Bischoff, H. *Eur. J. Clin. Invest.* **1994**, *24 Suppl 3*, 3.
7. Reuser, A. J.; Wisselaar, H. A. *Eur. J. Clin. Invest*. **1994**, *24 Suppl 3*, 19.
8. (a) Asano, N.; Ikeda, K.; Yu, L.; Kato, A.; Takebayashi, K.; Adachi, I.; Kato, I.; Ouchi, H.; Takahata, H.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2005**, *16*, 223. (b) Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036. (c) Ouchi, H.; Mihara, Y.; Takahata, H. *J. Org. Chem.* **2005**, *70*, 5207. (d) Kato, A.; Miyauchi, S.; Kato, N.; Nash, R. J.; Yoshimura, Y.; Nakagome, I.; Hirono, S.; Takahata, H.; Adachi, I. *Bioorg. Med. Chem.*, **2011**, *19*, 3558.
9. (a) Kato, A.; Hayashi, E.; Miyauchi, S.; Adachi, I.; Imahori, T.; Natori, Y.; Yoshimura, Y.; Nash, R. J.; Shimaoka, H.; Nakagome, I.; Koseki, J.; Hirono, S.; Takahata, H. *J. Med. Chem.* **2012**, *55*, 10347. (b) Natori, Y.; Imahori, T.; Murakami, K.; Yoshimura, Y.; Nakagawa, S.; Kato, A.;

Adachi, I.; Takahata, H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 738.
10. Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem. Eur. J.* **2006**, *12*, 6607.
11. Fu, G. C.; Zhou, J. S. *J. Am. Chem. Soc.* **2003**, *125*, 14726.
12. Puls, W.; Keup, U.; Krause, H. P.; Thomas, G.; Hoffmeister, F. *Naturwissenschaften,* **1977**, *64*, 536.
13. Experimental procedure: Male Wistar rats with a body mass of 130 g were obtained from Japan SLC, Inc. (Hamamatsu, Japan). Brush border membranes were prepared from the rat small intestines according to the method of Kessler et al.,[14] and were assayed at a pH of 6.8 for rat intestinal maltase, isomaltase, and sucrase using the appropriate disaccharides as substrates. The reaction mixture contained substrate (25 mM) and an appropriate amount of enzyme, and incubation was performed for 30 min at 37 ℃. The reaction was stopped by heating at 100 °C for 3 min. After centrifugation (600 xg; 10 min), the resulting reaction mixtures were added to Glucose CII-test Wako (Wako Pure Chemical Ind., Osaka, Japan). The absorbance at 505 nm was measured to determine the amount of D-glucose released.
14. Kessler, M.; Acuto, O.; Strelli, C.; Murer, H.; Semenza, G. A. *Biochem. Biophys. Acta*, **1978**, *506*, 136.