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The synthesis and biological evaluation of 1-*C*-alkyl-L-arabinoiminofuranoses, a novel class of α-glucosidase inhibitors

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ABSTRACT

The asymmetric synthesis of 1-*C*-alkyl-L-arabinoiminofuranoses **1** was achieved by asymmetric allylic alkylation (AAA), ring closing metathesis (RCM), and Negishi cross coupling as key reactions. Some of the prepared compounds showed potent inhibitory activities towards intestinal maltase, with IC_{50} values comparable to those of commercial drugs such as acarbose, voglibose, and miglitol, which are used in the treatment of type 2 diabetes. Among them, the inhibitory activity (IC_{50} = 0.032 μM) towards intestinal sucrase of **1c** was quite strong compared to the above commercial drugs.

A large number of compounds that mimic the structures of monosaccharides such as iminosugars have been isolated from plants and microorganisms.[1,2] Such sugar mimics have attracted considerable interest because of their ability to effectively and specifically inhibit various carbohydrate-degrading enzymes that are integral to a wide range of important biological processes, such as digestion,[3] the breakdown of hepatic glycogen,[4] the lysosomal catabolism of glycoconjugates,[5] and the maturation of the sugar chains in glycoproteins.[6] Although sugar mimics with inhibitory activities toward carbohydrate-degrading enzymes have potential for use as anti-diabetic, antiobesity, antiviral, and therapeutic agents for some genetic disorders, only a limited number of inhibitors, such as acarbose (Glucobay™), voglibose (Basen™), and miglitol (Glyset™) for the treatment of type 2 diabetes and miglustat (Zavesca™) as a therapeutic agent toward type 1 Gaucher disease, are currently on the market[7] (Fig. 1).

Accordingly, extensive efforts have been made in recent years to developing methodologies for the asymmetric syntheses of iminosugars.[8] However, the focus of many of these syntheses has been on derivatives of the D-form of the sugar. On the other hand, there are few reports of systematic studies of the biological properties of the L-enantiomers of iminosugars. As a continuation of our interests, we recently reported on the synthesis of both D- and L-enantiomers of iminosugars, as well as on their activities as glycosidase inhibitors.[9] This study reports on the synthesis of 1-alkyl iminofuranosides that contain alkyl groups substituted at the anomeric position. The replacement of the oxygen atom of an *N*,*O*-acetal function by a methylene group to form imino-*C*-glycosides has frequently been used as a tactic to generate stable analogs of glycoconjugates.[10] However, the chemistry of 1-*C*-alkyl iminofuranosides has been scarcely studied compared with investigations of 1-*C*-alkyl iminopyranosides.[11] Herein, we report on an asymmetric synthesis of 1-*C*-alkyl-L-arabinoiminofuranosides **1** and their activities as α-glucosidase inhibitors (Fig. 2).

Initially, the bicyclic 2,5-dihydropyrrole **2** was chosen as common intermediate for the synthesis of L-enantiomer **1**, since it can be prepared via the reaction of butadiene monoxide (**3**) and oxazolidinone (*R*)-**4**. The iodide **2** was prepared by iodination of oxazolidinonol **6**, which was obtained by a modified Trost procedure[12] using asymmetric allylic alkylation (AAA) and ring closing metathesis (RCM) as the key reactions (Scheme 1).

With the iodide **2** in hand, Csp^3–Csp^3 bond formation using metal-catalyzed cross coupling was examined owing to homologation of the alkyl substituents. Among the several procedures examined,[13] the Negishi cross coupling reaction developed by Fu and Zhou[14] successfully gave the desired alkyl substituted oxazolidinones **7** (Table 1).

The epoxidation of olefin in **7** with the dioxirane, generated in situ from oxone with 1,1,1-trifluoroacatone resulted in the stereoselective formation of the epoxides **8**, the stereochemistry of which was tentatively determined to *anti* with respect to the alkyl

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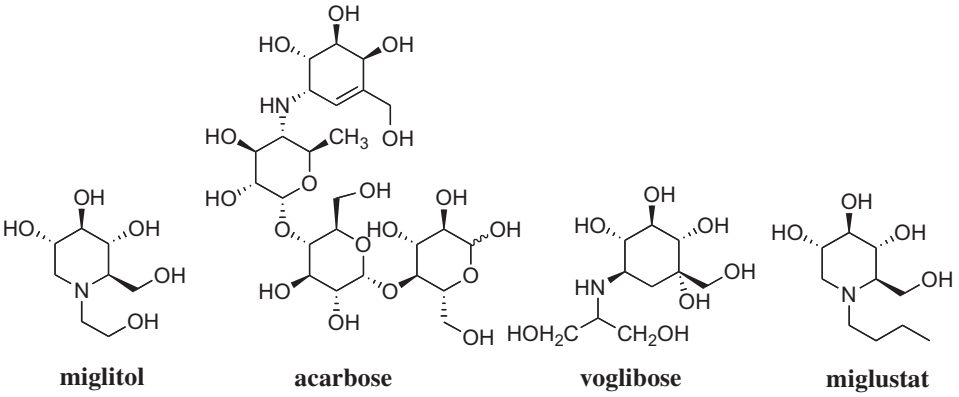


Figure 1. Commercial drugs of sugar mimics.

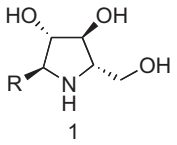


Figure 2. 1-*C*-Alkyl-L-arabinoiminofuranoses.

substituents. Ring opening of the epoxide with aqueous TFA provided the diols **9**, which were transformed by basic hydrolysis into the desired iminosugars **1**[11,15] (Scheme 2 and Table 2).

The enantiomers of **1c** and **1g** were next prepared by an AAA reaction with (*S*)-**4** using Trost's (*R*,*R*)-ligand via *ent*-**5c** and *ent*-**5g** in a similar manner to that described above (Scheme 3).

Having obtained the 1-*C*-alkyl-L-arabinoiminofuranoses **1**, their ability to serve as inhibitors of intestinal glucosidases was examined, since they could be of value in managing type 2 diabetes as demonstrated by the introduction of commercially available drugs (acarbose (Glucobay™), voglibose (Basen™), and miglitol (Glyset™)) based on this concept introduced for the management of type 2 diabetes.[18]

Among the above drugs, the iminosugar miglitol is an *N*-hydroxyethyl derivative of 1-deoxynojirimycin (DNJ) that delays the digestion of ingested carbohydrates, thereby resulting in a lower increase in blood glucose concentration following meals. Miglitol differs from acarbose and voglibose in that it is almost completely absorbed from the intestinal tract. Thus, miglitol has low-risk of causing hypoglycemia as a side effect. Furthermore, it should be pointed out that it may possess systemic effects in addition to its effects in the intestinal border.[19]

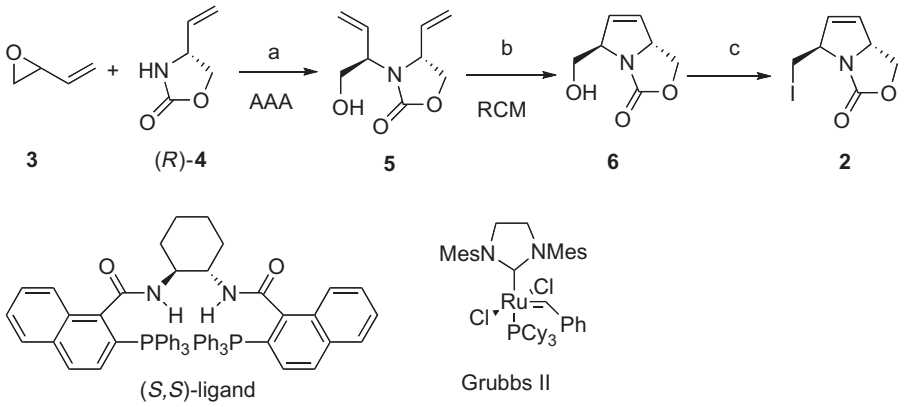
Table 1
Negishi cross coupling of **2** with alkylzinc halides using catalytic $Ni(COD)_2$ in the presence of a tridentate nitrogen ligand [(*R*,*R*)-*i*-Pr-Pybox]

Entry	R′ZnX	Product	Yield[a] (%)
1	CH_3ZnI	**7a**	69
2	CH_3CH_2ZnI	**7b**	63
3	$CH_3(CH_2)_2ZnBr$	**7c**	78
4	$CH_3(CH_2)_3ZnBr$	**7d**	63
5	$CH_3(CH_2)_4ZnBr$	**7e**	69
6	$CH_3(CH_2)_5ZnBr$	**7f**	69
7	$CH_3(CH_2)_6ZnBr$	**7g**	68
8	$CH_3(CH_2)_7ZnBr$	**7h**	72
9	$CH_3(CH_2)_8ZnBr$	**7i**	66
10	$CH_3(CH_2)_9ZnBr$	**7j**	71

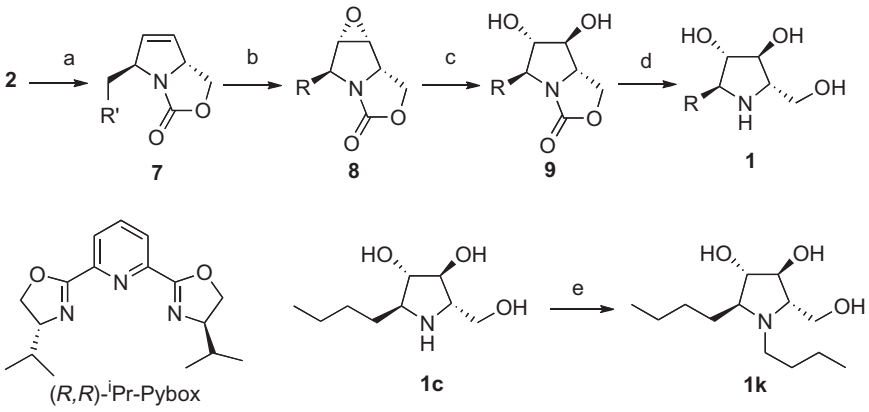
[a] Isolated yields.

We first investigated the influence of the absolute configuration of both enantiomers of **1c** and **1g** on glucosidase inhibition by comparing the IC_{50} values obtained for these with commercially available drugs. Surprisingly, the L-forms (**1c** and **1g**) showed quite potent inhibitory activity toward rat intestinal maltase, with IC_{50} values of 0.2 and 0.32 μM, respectively, while the activities of the D-forms (***ent*-1c** and ***ent*-1g**) were over 1000-fold weaker, as indicated in Table 3 (entries 3, 4, 8, and 9). The D-forms of iminosugars are typically much better inhibitors of α-glucosidase than the L-forms, except a few examples.[20] For example, while D-DNJ is an extremely powerful inhibitor of rat intestinal maltase, with IC_{50} values of 0.65 μM, the L-enantiomer was a 4000-fold weaker inhibitor than D-DNJ for this enzyme.[9f]

In the light of these results, a wide range of 1-*C*-alkyl-L-arabinoiminofuranoses **1a–j** bearing a linear alkyl chain (C_2–C_{11}) were



Scheme 1. Synthesis of common intermediate **2** for **1**. Reagents and conditions: (a) $[Pd_2dba_3]CHCl_3$, ligand, DBU, CH_2Cl_2, rt (91%); (b) Grubbs II, CH_2Cl_2, reflux (71%); (c) I_2, imidazole, Ph_3P, CH_2Cl_2 (88%).



Scheme 2. Synthesis of 1-*C*-alkyl-L-arabinoiminofuranoses **1** and *N*-butyl iminosugar **1k**. Reagents and conditions: (a) R′ZnX, $Ni(COD)_2$, (*R*,*R*)-*i*-Pr-Pybox, *N*,*N*-dimethylacetamide (DMA), rt; (b) CF_3COCH_3, oxone, $NaHCO_3$, CH_3CN-aq. EDTA, 0 °C (79–99%); (c) CF_3COOH, THF–H_2O (3:2), 80 °C (59–80%); (d) NaOH, C_2H_5OH–H_2O, 100 °C (57–87%); (e) *n*-$CH_3CH_2CH_2CHO$, $NaBH_3CN$, CH_3OH, rt (46%).

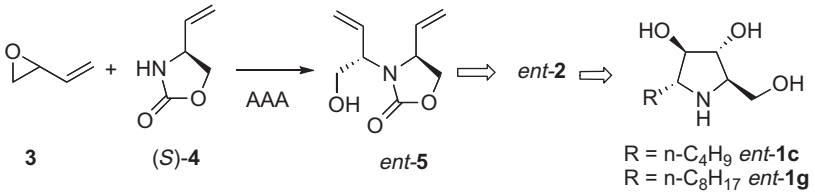
Table 2
Synthesis of iminosugars**1** from alkyl substituted oxazolidinones **7**

Entry	R	Product	Yield[a] (%)
1	CH_3CH_2	**1a**	51
2	$CH_3(CH_2)_2$	**1b**	58
3	$CH_3(CH_2)_3$	**1c**	43
4	$CH_3(CH_2)_4$	**1d**	52
5	$CH_3(CH_2)_5$	**1e**	55
6	$CH_3(CH_2)_6$	**1f**	59
7	$CH_3(CH_2)_7$	**1g**	35
8	$CH_3(CH_2)_8$	**1h**	49
9	$CH_3(CH_2)_9$	**1i**	30
10	$CH_3(CH_2)_{10}$	**1j**	45

The yields of three-step sequence from **7** to **1**.
[a] Isolated yields.

evaluated as α-glucosidase inhibitors (Table 3) since it seemed possible that selective inhibition could be achieved for this family of L-compounds.[11] We were pleased to observe, for α-glucosidase, a notable correlation between the chain length of the aglycone group and the inhibition values.

Interestingly, among the compound tested, the IC_{50} value (0.032 μM) found for **1c** for intestinal sucrase indicate that it is a dramatically more potent inhibitor than acarbose (Glucobay™), voglibose (Basen™), and miglitol (Glyset™). Inhibition towards intestinal sucrase and maltase of other 1-*C*-alkyl-L-arabinoiminofuranoses **1a**–**j** bearing linear alkyl chains (C_5–C_8) was roughly comparable to that of three commercially available drugs. However, inhibition for cases of iminosugars bearing short ($C_{2,3}$) and long (C_{9-11}) alkyl chains was substantially less. In particular, inhibition



Scheme 3. Synthesis of 1-*C*-alkyl-D-arabinoiminofuranoses.

Table 3
Inhibitory activities of intestinal glucosidases for **1**

Entry	Substrate	Maltase[a] IC_{50} (μM)	Isomaltase[a] IC_{50} (μM)	Sucrase[a] IC_{50} (μM)	Cellobiase[a]	Lactase[a]
1	**1a**	2.6	11	0.68	NI[b]	NI
2	**1b**	1.7	47	0.26	NI	NI
3	**1c**	0.2	4.7	0.032	NI	NI
4	*ent*-**1c**	NI	NI	392	NI	NI
5	**1d**	0.71	18	0.19	NI	NI
6	**1e**	0.51	11	0.11	NI	NI
7	**1f**	0.38	16	0.24	NI	NI
8	**1g**	0.32	75	0.45	NI	NI
9	*ent*-**1g**	500	NI	590	NI	NI
10	**1h**	0.84	171	1.4	NI	NI
11	**1i**	1.2	606	1.7	NI	NI
12	**1j**	3.9	NI	13	NI	NI
13	**1k**	25	NI	8.8	NI	NI
14	Acarbose	0.16	NI	2.9	NI	NI
15	Voglibose	0.18	5.2	0.37	NI	NI
16	Miglitol	0.59	39	1.0	NI	NI

Concentration of **1** for achieving 50% inhibition of rat intestinal glycosidases.[16]
[a] From rat intestine.
[b] NI: less than 50% inhibition at 1000 μM.

for **1h–j** with long (C_{9-11}) alkyl chains decreased regularly with the length of the attached alkyl chain. All of the produced 1-*C*-alkyl-L-arabinoiminofuranoses **1** were less effective inhibitors of intestinal isomaltase (an α-glucosidase that hydrolyses α-1,6-branching links in α-glucans) than for maltase and sucrase and this phenomenon was similar to that for the commercial drugs tested. In the case of the inhibition of β-glucosidases such as intestinal cellobiase and lactase, 1-*C*-alkyl-L-arabinoiminofuranoses **1** showed no inhibition (less than 50% inhibition at 1000 μM). Next, the *N*-butylated iminosugar **1k**[21] as an *N*-alkyl derivative of **1c** was prepared from **1c** and evaluated as a glucosidase inhibitor to examine the effect of a lipophilic group versus a hydrogen at the nitrogen. N-alkylated iminosugar **1k** was found to be much less efficient and less selective as an α-glucosidase inhibitor than the parent **1c** (entry 13). In view of these results, an alkyl chain at C-1 seems to be preferred for achieving suitable interactions with the putative lipophilic pocket and the hydrogen at the nitrogen also does to be important. However, the detailed reasons for this effect remain unclear.

In summary, a series of 1-*C*-alkyl-L-arabinoiminofuranoses **1** was prepared as potential α-glucosidase inhibitors. Their catalytic asymmetric synthesis was accomplished by asymmetric allylic alkylation (AAA), ring closing metathesis (RCM), and Negishi cross coupling as key reactions. Some of the alkyl iminofuranoses were found to be potent inhibitors of intestinal maltase, with IC_{50} values that were comparable to those of commercially marketed drugs such as acarbose, voglibose, and miglitol for the treatment of type 2 diabetes. Among them, compound **1c** also showed a greater inhibition against intestinal sucrase activity relative to the above commercial drugs. Since it is possible that Negishi cross coupling permits the insertion of a diversity of substituents at C1 of **1**, further studies of this aspect are currently in progress.

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15. Selected data: (2*S*,3*S*,4*S*,5*S*)-2-butyl-5-(hydroxymethyl)pyrrolidine-3,4-diol (**1c**): $[\alpha]_D^{27}$ −47.73 (*c* = 1.0, CH_3OH) ^1H NMR(400 MHz, CD_3OD) *δ*: 0.93 (3H, t, *J* = 6.8 Hz), 1.36–1.45 (6H, m), 1.71 (1H, m), 2.91 (1H, dd, *J* = 13.0, 7.7 Hz), 3.04 (1H, dd, *J* = 10.6, 6.3 Hz), 3.58–3.63 (2H, m), 3.68 (1H, dd, *J* = 11.6, 4.3 Hz), 3.77 (1H, t, *J* = 6.8 Hz).^{13}C NMR (100 MHz, CD_3OD) *δ*: 14.33, 23.77, 29.83, 34.45, 62.67, 62.87, 64.56, 79.13, 83.10.
16. *Experimental procedure:* Male Wistar rats with body weight of 130 g were obtained from Japan SLC, Inc. (Hamamatsu, Japan). Brush border membranes were prepared from the rat small intestine according to the method of Kessler et al.,[17] and were assayed at pH 5.8 for rat intestinal maltase, isomaltase, sucrase, cellobiase, and lactase using the appropriate disaccharides as substrates. The reaction mixture contained 25 mM substrate and the appropriate amount of enzyme, and the incubations were performed for 30 min at 37 °C. The reaction was stopped by heating at 100 °C for 3 min. After centrifugation (600*g*; 10 min), the resulting reaction mixture were added to the Glucose CII-test Wako (Wako Pure Chemical Ind., Osaka, Japan). The absorbance at 505 nm was measured to determine the amount of the released D-glucose.
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21. Compound **1k** was prepared by the reductive N-alkylation of **1c** with *n*-butylaldehyde in the presence of $NaBH_3CN$ in methanol.