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Enantiospecific Synthesis of Pseudoacarviosin as a Potential Antidiabetic Agent

Tony K. M. Shing,*,†,⊥ Hau M. Cheng,† Wai F. Wong,† Connie S. K. Kwong,† Jianmei Li,‡ Clara B. S. Lau,|| Po Sing Leung,§ and Christopher H. K. Cheng*,‡,⊥

Departments of Chemistry, Biochemistry, and Physiology, School of Pharmacy, and, Center of Novel Functional Molecules, The Chinese University of Hong Kong, Shatin, Hong Kong, China

tonyshing@cuhk.edu.hk (synthesis); chkcheng@cuhk.edu.hk (bioevaluation)

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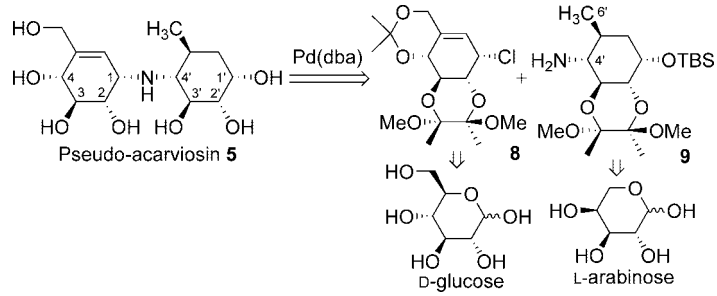
ABSTRACT



A pseudo-1,4′-*N*-linked disaccharide, pseudoacarviosin 5, was constructed via a key palladium-catalyzed coupling reaction of pseudoglycosyl chloride 8 (prepared from d-glucose via a novel direct intramolecular aldol addition in 12 steps) and pseudo-4-amino-4,6-dideoxy-α-d-glucose 9 (prepared from l-arabinose via an unusual *trans*-fused isoxazolidine-selective intramolecular nitrone−alkene cycloaddition in 11 steps). Pseudoacarviosin 5 has been shown to be a potent inhibitor of α-glucosidases, particularly the intestinal mucosal enzymes sucrase and glucoamylase of relevance to blood glucose control.

The therapeutic potential of sugar-mimetic glycosidase inhibitors for the treatment of diabetes, obesity, lysosomal storage diseases, cancer, and viral infections has stimulated demand for these compounds.[1] α-d-Glucosidase inhibitor acarbose **1** is a natural product that contains the pseudoaminosugar valienamine **2** as an indispensable component[2] for its bioactivity (Figure 1). Acarbose **1** is an orally active agent sold under the brand name Glucobay, Precose, or Prandase for the treatment of type 2 diabetes either on its own or in combination with other medications such as biguanides or sulfonylureas.[3] Hence, the design, synthesis, and bioevaluation of new α-d-glucosidase inhibitors[4] are highly warranted in order to obtain improved and more potent compounds for the treatment of hyperglycemia and related disorders.

Valienamine **2** itself is only a weak α-glucosidase inhibitor.[5] Its α-glucosidase inhibitory activity increases when it is linked to a di- or trisaccharide moiety as in adiposin-1 **3** and acarbose **1**, respectively.[6] On the other hand, methyl acarviosin **4**, obtained from the methanolysis of acarbose **1**, has been shown to exhibit stronger α-amylase inhibitory activity than **1**.[7]

Methyl acarviosin **4** contains valienamine **2** linked to an 6-deoxy-α-d-glucoside residue. Replacing the latter with a

† Department of Chemistry.
⊥ Center of Novel Functional Molecules.
‡ Department of Biochemistry.
|| School of Pharmacy.
§ Department of Physiology.

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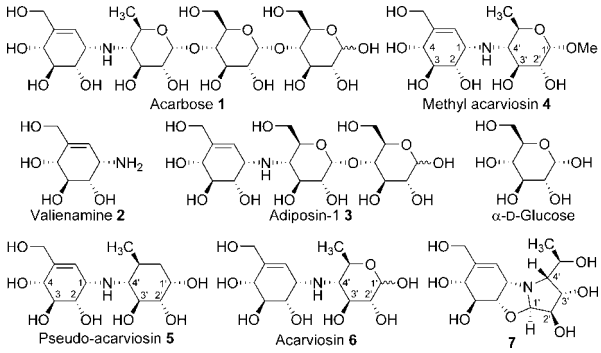


Figure 1. Structural relationship among acarbose, α-d-glucose, acarviosins, and pseudo-1,4′-*N*-linked disaccharides.

pseudoglucose moiety provides pseudoacarviosin **5**, a pseudo-1,4′-*N*-linked disaccharide with an α-d-*gluco*-configuration (except for the alkene C-5 carbon, carbohydrate numbering). Pseudoacarviosin **5** is a novel molecule that has not been considered or exploited as a glucosidase inhibitor. We postulated that **5** would be a more stable α-d-glucosidase inhibitor than **4** because the C-1′ in **5** is no longer an anomeric center and the OH-1′ configuration is therefore fixed and does not epimerize; hence, **5** is permanently locked in an α-d-glucosyl configuration. In contrast, the C-1′ glucosidic bond in **4** (and in acarbose) is prone to acid hydrolysis in the stomach, affording acarviosin **6**. It is not stable in its pyranose form and readily generates tricyclic compound **7**,[7] which does not produce the desired inhibitory effect.[8] The stability of **5** toward acid hydrolysis would produce a more sustained enzyme inhibition profile than **4**. Indeed, the newly synthesized pseudoacarviosin **5**, with half the molecular weight of acarbose, is shown in the present study to be a potent inhibitor of α-d-glucosidases of relevance to blood glucose level control, particularly toward the intestinal mucosal enzyme sucrase and glucoamylase.

The key step in the retrosynthesis of the target pseudoacarviosin **5** is the palladium-catalyzed coupling reaction[9] between the protected pseudoglycosyl chloride **8** and pseudo-4-amino-4,6-dideoxy-α-d-glucopyranose **9**, leading to the formation of the *N*-linkage (Figure 2). We have previously synthesized pseudosugars on the basis of transformation from (−)-quinic acid.[9,10] In the present investigation, we reveal efficient and innovative synthetic avenues for pseudosugar derivatives **8** and **9** from d-glucose and l-arabinose, respectively, the supply of which is inexpensive and virtually unlimited.[11]

The synthesis of the coupling precursor **9** is presented first. There has been no report on synthetic studies toward pseudo-

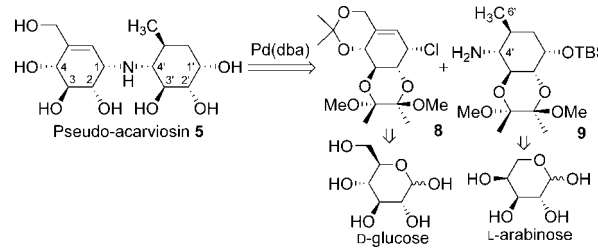
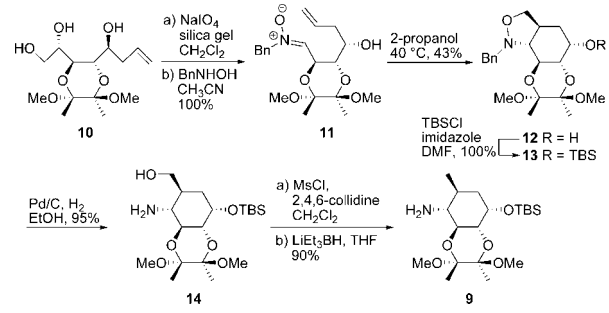


Figure 2. Retrosynthesis of pseudoacarviosin **5**.

4-amino-4,6-dideoxy sugars, the right-hand portion of the target molecule.[6b] This paper discloses a novel approach toward **9** via an unusual *trans*-fused isoxazolidine-selective intramolecular nitrone−alkene cycloaddition (INAC)[12] as the key step (Scheme 1). Thus, *trans*-diacetal **10** was readily

Scheme 1



obtained from l-arabinose in four steps with 56% overall yield according to our recent endeavor.[13] Oxidative *vic*-diol cleavage[14] of **10** followed by reaction with BnNHOH generated nitrone **11** quantitatively. INAC of nitrone **11** gave, inter alia, the desired *trans*-fused isoxazolidine **12** in 43% isolated yield. The stereoselective formation of the *trans*-fused isoxazolidine **12** along with lesser amounts of three other stereoisomers, controlled by the *trans*-diacetal blocking group of the nitrone,[12] is noteworthy because nitrones with *cis*-acetonides and with benzyl protecting groups generally afford *cis*-fused isoxazolidines.[15] The structure of **12** was confirmed by X-ray crystallography. Silylation of **12** provided silyl ether **13** that underwent hydrogenolysis of the

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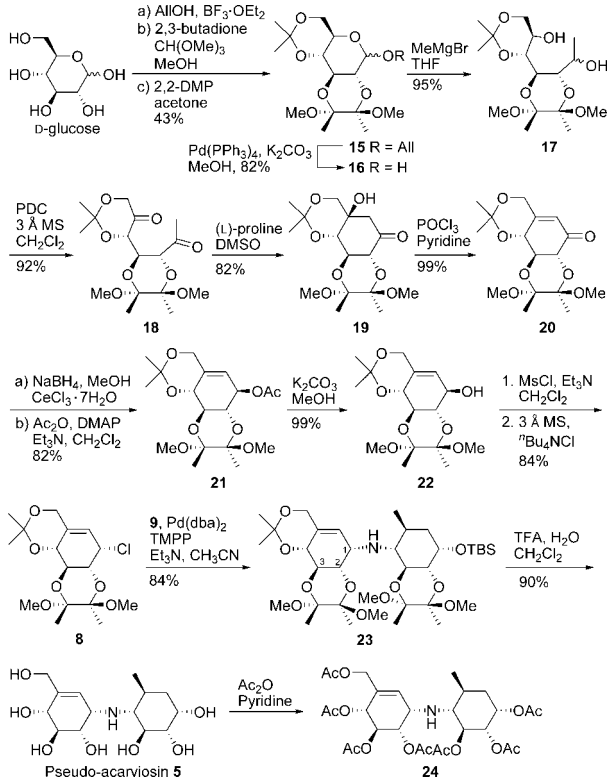
N−O linkage and the *N*-benzyl group to give amino alcohol **14** efficiently. Regioselective mesylation[16] of the hydroxyl group in **14** followed by hydride displacement of the resultant mesylate gave **9** in 90% overall yield from **14**. Hence, the coupling precursor **9** was made from l-arabinose in 11 steps with an overall yield of 21%.

Synthesis of pseudoglycosyl chloride **8**, the left-hand portion of the target molecule, was accomplished by a novel carbocyclization of d-glucose involving a direct intramolecular aldol addition as the key step. Glycosidation of d-glucose produced a mixture of α- and β-d-allyl pyranosides that were *trans*-2,3-*O*-acetalized[17] and then 4,6-*O*-isopropylidenated to give the fully protected glycosides **15** in 43% overall yield (Scheme 2). Palladium-catalyzed deallylation[18]

Scheme 2



of glycosides **15** furnished lactols **16** that were subjected to Grignard methyl addition to give the diols **17** efficiently. Oxidation of **17** furnished 1,5-diketone **18** that underwent l-proline-catalyzed intramolecular aldol addition[19,20] to generate β-hydroxyl ketone **19** smoothly in 82% yield. This is in fact the first report of a direct intramolecular aldol addition of a ketone(acceptor)−ketone(donor) derived from d-glucose. The structure of **19** was confirmed by X-ray crystallography. Elimination of the tertiary alcohol in **19** with $POCl_3$[21] afforded enone **20** almost quantitatively. Luche reduction[22] of enone **20** provided a mixture of diastereomeric allylic alcohols which were acetylated to give a mixture of acetates, separable on chromatography. Thus, β-acetate **21** was isolated pure in 82% overall yield from enone **20**. Deacetylation of **21** gave β-alcohol **22** in excellent yield. Mesylation of **22** followed by nucleophilic displacement with tetrabutylammonium chloride provided the desired α-allylic chloride **8** smoothly. The protected pseudoglycosyl chloride **8** was thus synthesized from d-glucose in 12 steps with an overall yield of 16.9%.

Palladium-catalyzed coupling reaction[23] of allylic chloride **8** and amine **9** produced a pseudo-1,4-aminodisaccharide in 84% yield. Three equivalents of amine **9** were required in order to give good yields of the adduct, and fortunately, most of the excess amine **9** was recovered. Our previous work[9] has already optimized the reaction conditions on similar substrates and reported that acetal blocking groups were ideal for this type of reaction that proceeded with retention[23] of configuration. The ^{1}H NMR spectrum of **23** displays $J_{1,2} = 5.1$ Hz and $J_{2,3} = 10.8$ Hz, indicating that H_1 and H_2 are still *cis*-disposed after the coupling reaction and the structure is therefore assigned as protected pseudoacarviosin **23**. Complete deprotection of **23** was achieved in one step under mild acid hydrolysis to give the target compound **5** which was characterized as its corresponding heptaacetate **24**. Pseudoacarviosin **5** was thus made from d-glucose in 14 steps with 12.7% overall yield.

Pseudoacarviosin **5** was demonstrated to exhibit strong inhibitory actions against various α-glucosidases including α-amylase from human saliva and α-glucosidases (maltase, sucrase, isomaltase, glucoamylase) from the small intestine of rat. Enzyme inhibition by **5** was in a dose-dependent manner, and the order of inhibition on the enzymes was glucoamylase > sucrase > maltase > α-amylase > isomaltase. Inhibition toward sucrase and glucoamylase was particularly potent, with IC_{50} values of 3.9×10^{-7} M and 1.2×10^{-7} M, respectively (Table 1). Compared with acarbose **1**, pseudoacarviosin **5** is a better sucrase inhibitor. Inhibition of sucrase by pseudoacarviosin **5** was demonstrated to be reversible by simple dilution and dialysis. Preliminary in vivo studies on diabetic rats indicates that **5** is an orally active specific inhibitor of α-glucosidases and exhibits more potent effect than acarbose in sucrose loading test and could significantly lower increase in blood glucose level of diabetic

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Table 1. IC_{50} Values (Expressed in M) of the Inhibition of Digestive Enzymes by Pseudoacarviosin **5** As Compared with Acarbose **1**

enzyme	pseudoacarviosin **5**	acarbose **1**
α-amylase	5.1×10^{-5}	2.5×10^{-6}
maltase	1.6×10^{-5}	2.7×10^{-6}
sucrase	3.9×10^{-7}	0.9×10^{-6}
trehalase	no inhibition	no inhibition
isomaltase	1.3×10^{-4}	1.0×10^{-4}
glucoamylase	1.2×10^{-7}	1.6×10^{-7}

rats even at 0.02 mg/kg. Investigation is still underway and the results will be published in a full paper.

In conclusion, the results suggest that **5** could be used in the treatment of type 2 diabetes by lowering postprandial blood glucose level. It is particularly useful in inhibiting the digestion of table sugar, and provides an important lead for the design of antidiabetic drugs in view of the importance of postprandial glycemic control in the pathological development of diabetes.[24] The synthetic chemistry that involves novel transformation of carbohydrates into carbocycles, especially the ketone−ketone intramolecular direct aldol addition, could be exploited for a wide range of functionalized cyclohexenoid or cyclohexanoid targets and intermediates of pharmaceutical importance, including a new synthesis of Tamiflu,[11] which is a functionalized cyclohexene used in the treatment of avian flu.

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Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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