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Stereoselective synthesis of (+)-5-thiosucrose and (+)-5-thioisosucrose†

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(+)-5-Thiosucrose **1**, a novel isosteric sulfur analog of sucrose, was synthesized stereoselectively for the first time *via* indirect β -D-fructofuranosidation involving selective β -D-psicofuranosidation, followed by stereo-inversion of the secondary hydroxy group at the C-3 position on the furanose ring. Glycosidation of protected 5-thio-D-glucose with a D-psicofuranosyl donor provided β -D-psicofuranosyl 5-thio- α -D-glucopyranoside and that with D-fructofuranosyl donor gave α -D-fructofuranosyl 5-thio- α -D-glucopyranoside. Two anomeric stereocenters of the glycosyl donor and acceptor were controlled correctly to provide a single disaccharide among four possible anomeric isomers in the glycosylation. Conversion of the resulting disaccharides afforded (+)-5-thiosucrose **1** and (+)-5-thioisosucrose **2** in excellent yields, respectively. Inhibitory activities of **1** and **2** against α -glucosidase *in vitro* were also examined.

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Introduction

Sucrose (Fig. 1) is one of the common sugars in nature and is an important carbohydrate for energy source in human health. At the same time, it is also a favorite sweetener in our daily life. So far, a variety of synthetic analogs of sucrose have been synthesized as low- or noncalorie alternatives for a healthy dietary

purpose. For example, sucralose (Splenda®) is a widely known analog of sucrose in which three hydroxy groups are replaced by chlorine atoms, leading to a hundredfold increase in sweetness compared to that of sucrose.¹ Many other derivatives of sucrose with different substituents have also been reported.² However sucrose analogs in which an atom in the sucrose ring system is changed are far less common. As rare examples, C-sucrose, in which the glycosidic oxygen is replaced by a carbon atom, was synthesized by Kishi *et al.*, and hemicarbasucrose, a carba-analog of sucrose, was reported by Jiménez-Barbero and Sollogoub *et al.*³ Although sucrose is an actual substrate for α -glucosidase, these modified sucrose analogs are not substrates of α -glucosidase and non-notable activities in inhibition against α -glucosidase were reported.

Thiosugars replace a ring oxygen atom with a sulfur atom in carbohydrate, and are extremely rare in nature with the exception of 5-thio-D-mannose⁴ and salacinols.⁵ It should be noted that salacinol has potent enzymatic inhibitory activity against α -glucosidase. In fact, it has been already approved and used commercially in the context of dietary drinks or supplement of foods. Hetero monosaccharides, including thiosugars,⁶ azasugars,⁷ and carbasugars,⁸ and their disaccharide analogs⁹ have been synthesized as sugar mimics and their biological behaviors and functions involving α -glucosidase inhibitory activity were examined.¹⁰ However, there has been nothing potent beyond salacinol concerning α -glucosidase inhibition.^{11,12}

α -Glucosidase hydrolyzes sucrose to fructose and glucose, and interestingly, 5-thio-D-glucose inhibits this process.^{11af} A pyranose ring oxygen is essentially required for the substrates of α -glucosidase.¹³ As an isosteric analog of sucrose, 5-thiosucrose **1** and 5-thioisosucrose **2** possesses a 5-thioglucose moiety and

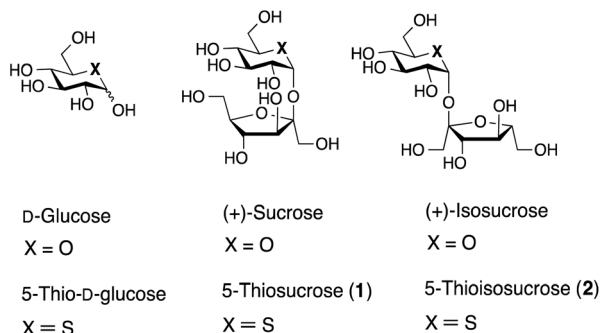


Fig. 1 Structures of glucose, sucrose, isosucrose, and their sulfur analogs.

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would resemble the conformation of sucrose. We thought that **1** would be of interest as a sweetener as well as an inhibitor superior than 5-thio-D-glucose. This research is focused on the stereoselective synthesis of 5-thiosucrose **1** and 5-thioisucrose **2**, and herein we report their synthesis and some biological properties.

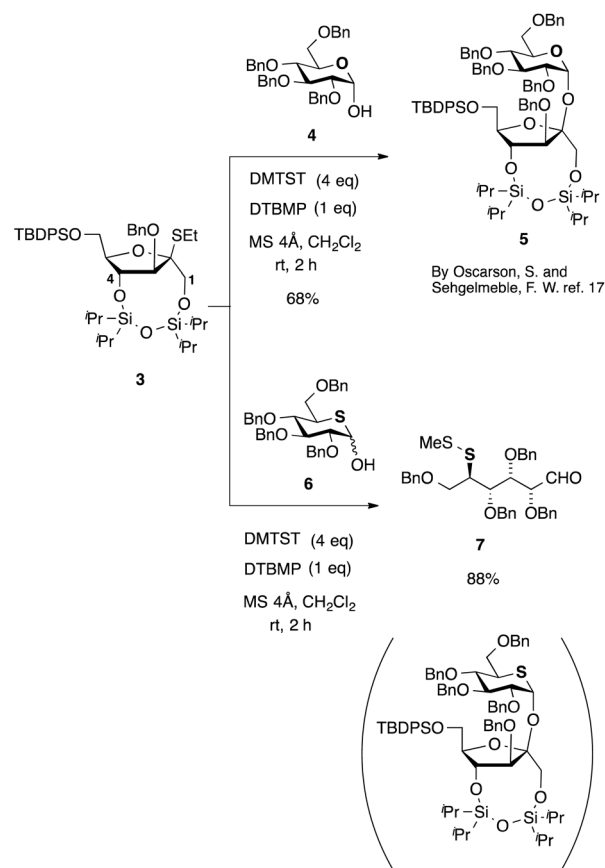
Results and discussion

Although many methods for the stereoselective glycosylation have been reported and utilized,¹⁴ early attempts at the synthesis of sucrose¹⁵ revealed the difficulties involved with the stereocontrol of its two anomeric centers. For the synthesis of **1** and **2**, two anomeric carbon centers connected with β,α - and α,α -O-linkage [**1**; β -D-Fruf(2 \leftrightarrow 1)- α -D-Glcp and **2**; α -D-Fruf(2 \leftrightarrow 1)- α -D-Glcp] need to be controlled in a glycosylation step. An α -selectivity rather than β -selectivity was reported for glycosylation of D-fructose as an either glycosyl acceptor or donor.^{14a} In fact, glycosylation of D-fructofuranose affords an α -anomer or α -predominant mixtures in most cases.¹⁶ On the other hand, 5-thio-D-glucose has been used as a glycosyl donor to form an α -glycosidic bond by the anomeric effect of the sulfur ring.⁶ However, it has never been used as an acceptor in glycosylation reaction to our best knowledge.

Despite these failures in β -D-fructofuranosylation, the natural occurrence of β -D-furanoside can be found in sucrose and inulin. Therefore, β -directing D-fructofuranosylation has been a challenging task and this has encouraged carbohydrate chemists to develop selective β -D-fructofuranosylation. There is only one elegant example in β -D-fructofuranosylation, reported by Oscarson *et al.*¹⁷ As shown in Scheme 1, they used ethyl thioglycoside **3** as a D-fructofuranosyl donor, in which the C-1 and C-4 hydroxy groups are fixed with a connection of cyclic disiloxether to block an attack from the α -face of the furanose ring. Stereoselective glycosylation of the acceptor **4** with **3** promoted by dimethyl(methylthio)sulfonium triflate (DMTST) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) and 4 Å molecular sieves occurred to give β -furanosyl α -pyranoside **5** with 68% yield, exclusively.^{17a}

Accordingly, we initially attempted the Oscarson's method for the synthesis of **1**. However, glycosylation of 2,3,4,6-tetra-O-benzyl-5-thio-D-glucopyranose (**6**)¹⁸ with **3** gave no desired disaccharide. Instead, disulfide **7** was isolated in 88% yield. Activation of sulfide by DMTST occurred on the *endo*-sulfide of the acceptor **6** instead of the *exo*-sulfide of the donor **3**. Therefore, this method could be useful for general oxygen sugars but not for thiosugars.

Since Oscarson's β -D-fructofuranosylation method was found to be incompatible with the synthesis of **1**, we turned our attention to indirect synthesis through β -D-psicofuranosylation, which was employed in the stereoselective synthesis of sucrose previously.¹⁹ We have reported that glycosylation of D-glucopyranose with D-psicofuranosyl donor²⁰ protecting 3,4-diols with acetonide gave β -D-psicofuranosyl α -D-glucopyranoside, which afforded sucrose after several steps. D-Psicofuranosyl donor was regarded as β -D-fructofuranosyl donor in the disaccharide syntheses.^{19,21} On the other hand, glycosylation of D-



Scheme 1 Reaction of Oscarson's glycosyl donor **3** with acceptors **4** and **6**.

glucopyranose with D-fructofuranosyl donor occurred to give α -D-fructofuranosyl α -D-glucopyranoside predominantly which was used for the synthesis of isosucrose. The course of α -D-fructofuranosylation or β -D-psicofuranosylation could be governed by the stereochemistry of the C-3 hydroxy substituent. Glycosylation of acceptor with D-fructofuranosyl donor is not sufficient for the syntheses of β -D-fructofuranosides, but is suitable for α -D-fructofuranoside. Based on the above results, synthetic plan for **1** and **2** is depicted in Fig. 2.

D-Fructofuranosyl donor with 5-thioglucoceptor would give α -D-fructofuranosyl 5-thio- α -D-glucopyranoside, of which anomeric centers would matched with the stereochemistry of **2**. Glycosylation of 5-thioglucoceptor with D-psicofuranosyl donor would give β -D-psicofuranosyl 5-thio- α -D-glucopyranoside of which anomeric centers would matched with the stereochemistry of **1**. This disaccharide will lead to **1** after a stereo-inversion at the C-3 hydroxy group. In both cases, α -glycoside on the anomeric center of 5-thioglucoceptor would be formed by the strong anomeric effect of the thiane ring.

Synthesis of 5-thioisucrose (**2**)

Several D-fructofuranosyl donors are available. Fructofuranosyl halide,^{16a} fructofuranosyl phosphite,^{16c} 2-O-acetylfructofuranose,^{16e} 2-thiofructofuranoside,^{16d} and fructofuranosyl *N*-phenyltrifluoroacetimidate^{16f} have been reported. Nevertheless,



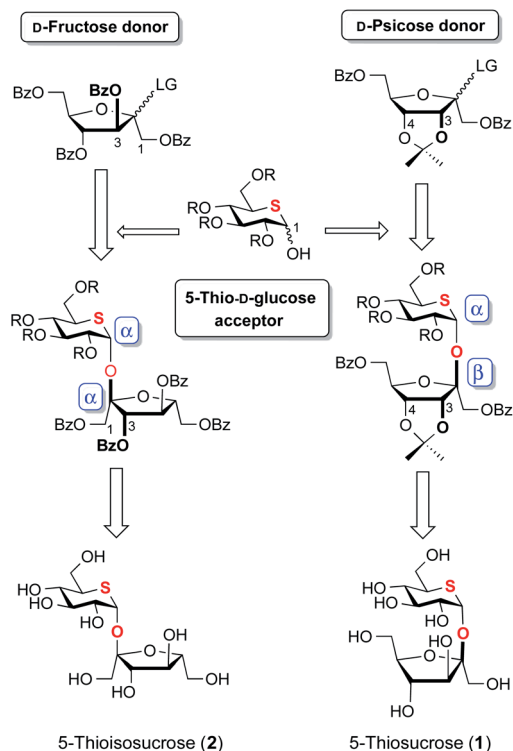
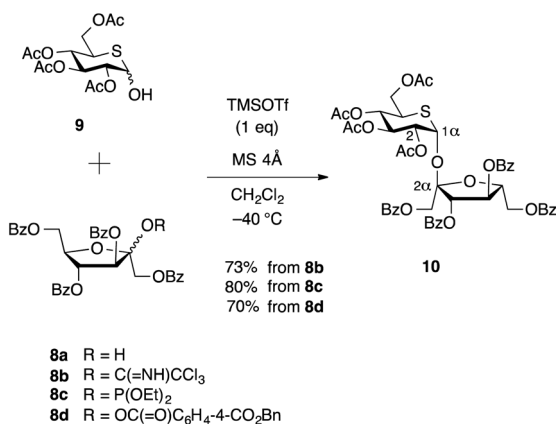


Fig. 2 Synthetic plan for 5-thiosucrose 1 and 5-thioisoscrose 2.

most of these glycosidations entail synthetic difficulties since *D*-fructose possesses a sterically congested anomeric hydroxy group due to the structure of ketohexofuranose. In addition, the choice of leaving groups is restricted in this case because a sensitive cyclic sulfide unit exists in the glycosyl acceptor for the synthesis of 2.

As shown in Scheme 2, we examined three different *D*-fructofuranosyl donors, thus imidate donor²² **8b**, phosphite donor **8c**,^{16c} and benzyl phthalate donor²³ **8d**. These donors were prepared from 1,3,4,6-tetra-*O*-benzoyl-*D*-fructofuranose (**8a**).^{16b} Trimethylsilyl trifluoromethanesulfonate (TMSOTf) promoted glycosylation of 2,3,4,6-tetra-*O*-acetyl-5-thio-*D*-glucose **9** (ref. 18)



Scheme 2 α -*D*-Fructofuranosylation of 5-thio-*D*-glucopyranose 9.

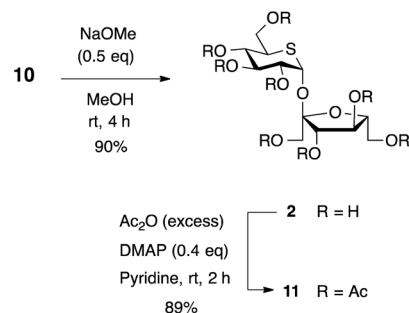
with each glycosyl donor **8b**, **8c**, or **8d**²⁴ at -40 °C in dichloromethane in the presence of 4 Å molecular sieves resulted in the formation of 2 α ,1 α -disaccharide **10** [α -*D*-Fru α (2 \leftrightarrow 1)- α -*D*-Glc β] as a single isomer with 73%, 80%, and 70% yields, respectively. It is noteworthy that a single isomer (2 α ,1 α) was formed exclusively among the four possible anomeric isomers (2 β ,1 α , 2 α ,1 α , 2 α ,1 β , and 2 β ,1 β) in this glycosidation, while *D*-glucopyranosyl acceptor reported in the synthesis of isosucrose produced two anomeric isomers (2 α ,1 α , 2 α ,1 β) in moderate selectivities (47 : 53,^{16a} 4 : 1,^{16c} and 84 : 16 (ref. 16e)). Although the three fructofuranosyl donors used in this study showed similar reactivity and selectivity, phthalate donor **8d** is regarded as the most convenient donor because it is readily prepared and stable under storage, in comparison with other donors **8b** and **8c**.

Stereochemistry at the anomeric positions in **10** was determined by the coupling constant in the ¹H NMR spectrum and the chemical shifts in the ¹³C{¹H} NMR spectrum. The *J*_{1,2} value of the pyranose ring proton is 3.1 Hz, which is in the typical value of α -glucopyranoside, and it is identical to that of 1,2-*cis*- α -*D*-glucopyranoside. The ¹³C{¹H} NMR chemical shift of the anomeric position of the furanose ring exhibits at 109.0 ppm, which is identified to that of α -*D*-fructofuranoside.^{17a,25} These data supported the structure of the disaccharide **10**.

Finally, treatment of **10** with NaOMe in MeOH furnished the synthesis of **2** in 90% yield (Scheme 3). Compound **2** was synthesized in two steps from *D*-fructose donor with strict stereocontrol of two anomeric centers. The corresponding octaacetate **11** was prepared in 89% yield in order to compare the analytical data with the related disaccharides shown in Table 1.

Synthesis of 5-thiosucrose (1)

According to the synthetic plan, we started the synthesis of **1** through β -*D*-psicofuranosidation. The initial step of this synthesis involved β -selective glycosidation of **6** with the *O*-protected *D*-psicofuranosyl donor **12**,^{18,19,24} which was prepared from *D*-psicose in 49% overall yield in five steps.^{20b} Reaction of **6** with **12** in the presence of TMSOTf in dichloromethane at -40 to -20 °C afforded the desired glycoside **13** in 76% yield as a single stereoisomer (Scheme 4). The configuration of the anomeric center on the pyranoside ring in **13** was identified as that of α -*D*-glucopyranoside by a *J*_{1,2} value of 2.9 Hz. The anomeric center in *D*-psicofuranoside was identical to β -



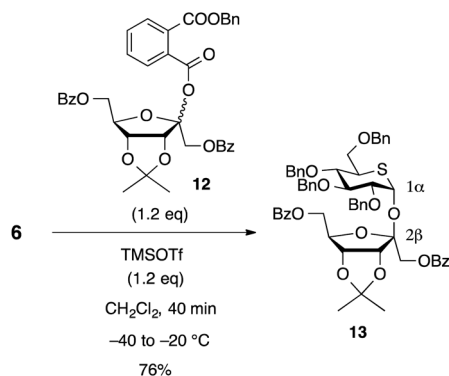
Scheme 3 Synthesis of 5-thioisoscrose 2 and its acetate 11.



Table 1 Comparison of octaacetyl disaccharides **18**, **11**, **19**, and **20**

Compound	Specific rotation ^a [α] _D	Chemical shifts of furanose protons ^b (δ)							Coupling constants of furanose protons ^b (Hz)			
		H-1a	H-1b	H-3	H-4	H-5	H-6a	H-6b	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$
18	+67.6	4.38	4.28	5.71	5.62	4.22	4.52	4.52	5.9	5.6	5.5	5.5
11	+147.8	4.52	4.29	5.69	4.87	4.55	4.54	4.30	0.5	3.3	4.1	7.7
19 ^c	+60.0	4.37	4.29	5.71	5.55	4.20	4.41	4.41	5.4	5.7	5.4	5.4
20 ^c	+83.5	4.79	3.98	5.69	4.84	4.45	4.39	3.96	1.0	3.0	4.0	2.0

^a CHCl₃ was used as a solvent. ^b Benzene-*d*₆ was used as a solvent. ^c These values were obtained from the literature.³⁰

Scheme 4 Psicofuranosylation with 5-thio- α -D-glucopyranose **6**.

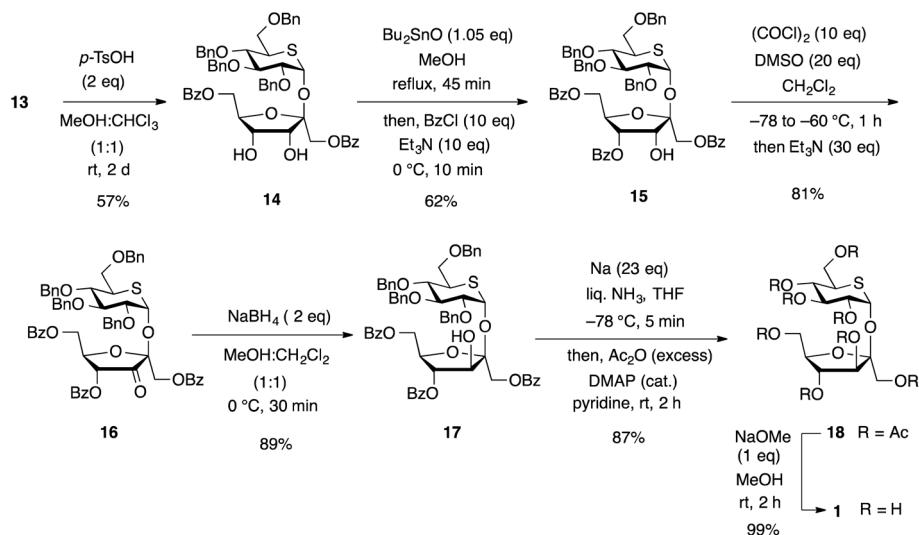
glycoside. In general, the C2-carbon of psicofuranoside appears between 107–109 ppm for β anomers and between 103–105 ppm for α anomers,^{19,20} and the ¹³C{¹H} NMR chemical shift of the anomeric carbon existed at 109.9 ppm in **13**.

In this reaction, protected 5-thioglucofuranose **6** performed an α -directing acceptor as same as **9** in the synthesis of 5-thio-isosucrose. The glycosidation occurred on the β -face of the furanose donor **12** because of the steric influence of the

acetonide group existing on the α -side of the ring. Considering that *D*-psicofuranosylation of the corresponding α -*D*-glucose gave a mixture in the ratio of 2 : 1 (α -glucopyranoside vs. β -glucopyranoside),¹⁹ it should be noted that the predominant selectivity for 5-thio-*D*-glucopyranose **6** vs. *D*-glucopyranose is quite interesting in psicofuranosylation of 5-thiopyranose and pyranose donors.²⁶

Conversion of β -*D*-psicofuranoside **13** to β -*D*-fructofuranoside **17** was carried out in four steps (Scheme 5):

Deprotection of acetonide group in **13** with *p*-toluenesulfonic acid in MeOH gave diol **14** in 57% yield. Benzoate **15** was obtained from **14** via a stannylene intermediate. Treatment of **14** with Bu₂SnO in MeOH at reflux temperature followed by benzylation on the C-4 hydroxy group with benzoyl chloride gave **15** selectively.²⁷ The Swern conditions will be a choice for oxidation of the secondary hydroxy group in the presence of cyclic sulfide. The secondary alcohol of **15** was oxidized smoothly to give ketone **16** in 81% yield. Then, reduction of the ketone **16** with NaBH₄ occurred from the bottom of the furanose ring selectively to convert to β -*D*-fructofuranoside **17** in 89% yield. The direction of hydride attack in the reduction of 3-ketone is controlled by the adjacent 2- β -glycosidic bond to give 2,3-*syn*-product.²⁸ Removal of both O-benzoyl and O-benzyl groups in disaccharide **17** under the Birch conditions and

Scheme 5 Synthesis of **1**.

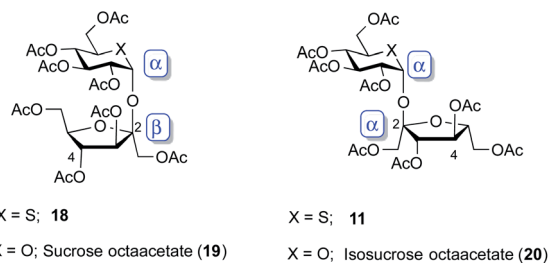


Fig. 3 Octaacetate of 5-thiosucrose **18**, 5-thioisoscrose **11**, sucrose **19**, and isosucrose **20**.

successive acetylation gave octaacetate **18** in 87% yield. After deprotection of all acetyl groups under Zemplén's conditions,²⁹ the synthesis of **1** was accomplished in 99% yield.

Stereochemistry

The specific rotations, and chemical shifts and coupling constant of ¹H NMR for octaacetates of 5-thiosucrose and 5-thioisoscrose (**18** and **11**) are summarized with the corresponding data reported for sucrose and isosucrose (**19** and **20**)³⁰ in Table 1. Their structures are shown in Fig. 3. Specific rotation values of 5-thioisoscrose and isosucrose (**11** and **20**) are relatively larger than those of 5-thiosucrose and sucrose (**18** and **19**). Chemical shifts of each α,α -anomers (**11** and **20**) and those of β,α -anomers (**18** and **19**) are comparable in ¹H NMR. The chemical shifts of the H-4 protons in furanose ring are characteristic. Their difference (*ca.* 0.7 ppm) can be observed between **19** and **20**, and thioanalogs **18** and **11**. Coupling constants of $J_{3,4}$ and $J_{4,5}$ in sucrose **19** and thiosucrose **18** are larger than those of isosucrose **20** and thioisoscrose **11**. Thus, all these results supported the structures of 5-thiodisaccharides **11** and **18**.

Biological study

Inhibitory activities against α -glucosidase for compounds **1**, **2**, and 5-thio-D-glucose were examined *in vitro* using rat intestinal α -glucosidase. In literature, 5-thio-D-glucose is reported to be a weak to moderate inhibitor for α -glucosidase.^{11f,12} In the present study, 5-thio-D-glucose showed 48% inhibition at 8 mM. It was regrettable that neither **1** nor **2** exhibited any inhibition at 8 mM, while commonly used α -glucosidase inhibitor such as acarbose and voglibose work at nM levels. Although 5-thio-D-glucose has a sweet taste, **1** was found to be a little bitter rather than sweet, in rough-and-ready taste analyses.

Conclusions

The first stereoselective syntheses of **1** and **2** were achieved by stereoselective glycosidation. The key steps involved D-fructofuranosylation and D-psicofuranosylation of protected 5-thio-D-glucose acceptors **9** and **6** to afford α -D-fructofuranosyl 5-thio- α -D-glucopyranoside **10** and β -D-psicofuranosyl 5-thio- α -D-glucopyranoside **13** with high stereoselectivity in excellent yields, respectively. The configurations of their two-anomeric centers

were strictly controlled in a single glycosidation step, in which the strong anomeric effect of 5-thio-D-glucopyranose was observed. We have demonstrated that 5-thio-D-glucopyranose works as an α -directing glycosyl acceptor for the first time. Although neither **1** nor **2** exhibit α -glucosidase inhibitory activity or sweetness, current results will aid in the design of new α -glucosidase inhibitors and the synthesis of other disaccharide of thiosugar derivatives.

Conflicts of interest

There are no conflicts to declare.

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