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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  $\beta$ -D-fructofuranosidation involving selective  $\beta$ -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  $\beta$ -D-psicofuranosyl 5-thio- $\alpha$ -D-glucopyranoside and that with D-fructofuranosyl donor gave  $\alpha$ -D-fructofuranosyl 5-thio- $\alpha$ -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  $\alpha$ -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.<sup>1</sup> Many other derivatives of sucrose with different substituents have also been reported.<sup>2</sup> 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.*<sup>3</sup> Although sucrose is an actual substrate for  $\alpha$ -glucosidase, these modified sucrose analogs are not substrates of  $\alpha$ -glycosidase and non-notable activities in inhibition against  $\alpha$ -glycosidase 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-mannose<sup>4</sup> and salacinols.<sup>5</sup> It should be noted that salacinol has potent enzymatic inhibitory activity against  $\alpha$ -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,<sup>6</sup> azasugars,<sup>7</sup> and carbasugars,<sup>8</sup> and their disaccharide analogs<sup>9</sup> have been synthesized as sugar mimics and their biological behaviors and functions involving  $\alpha$ -glucosidase inhibitory activity were examined.<sup>10</sup> However, there has been nothing potent beyond salacinol concerning  $\alpha$ -glucosidase inhibition.<sup>11,12</sup>

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

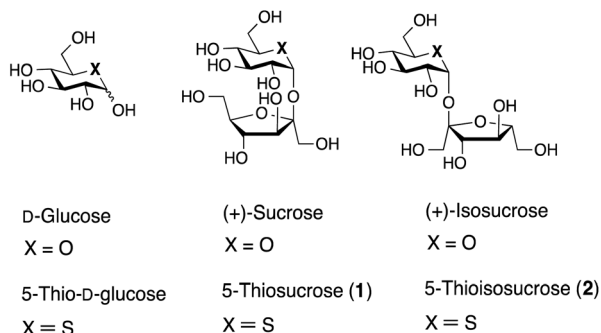


Fig. 1 Structures of glucose, sucrose, isosucrose, and their sulfur analogs.

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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.

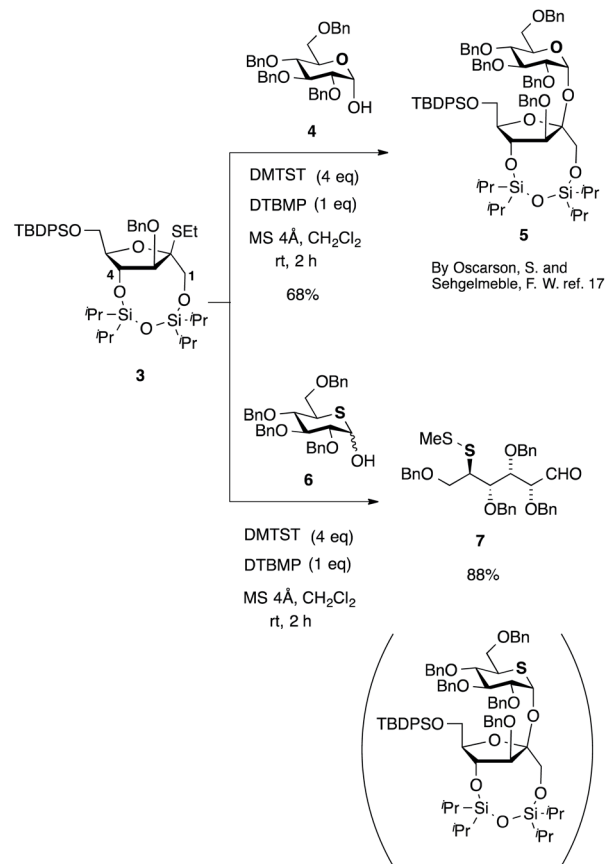
## Results and discussion

Although many methods for the stereoselective glycosylation have been reported and utilized,<sup>14</sup> early attempts at the synthesis of sucrose<sup>15</sup> 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  $\beta,\alpha$ - and  $\alpha,\alpha$ -O-linkage [**1**;  $\beta$ -D-Fruf-(2  $\leftrightarrow$  1)- $\alpha$ -D-Glcp and **2**;  $\alpha$ -D-Fruf-(2  $\leftrightarrow$  1)- $\alpha$ -D-Glcp] need to be controlled in a glycosylation step. An  $\alpha$ -selectivity rather than  $\beta$ -selectivity was reported for glycosidation of D-fructose as an either glycosyl acceptor or donor.<sup>14a</sup> In fact, glycosidation of D-fructofuranose affords an  $\alpha$ -anomer or  $\alpha$ -predominant mixtures in most cases.<sup>16</sup> On the other hand, 5-thio-D-glucose has been used as a glycosyl donor to form an  $\alpha$ -glycosidic bond by the anomeric effect of the sulfur ring.<sup>6</sup> However, it has never been used as an acceptor in glycosidation reaction to our best knowledge.

Despite these failures in  $\beta$ -D-fructofuranosylation, the natural occurrence of  $\beta$ -D-furanoside can be found in sucrose and inulin. Therefore,  $\beta$ -directing D-fructofuranosylation has been a challenging task and this has encouraged carbohydrate chemists to develop selective  $\beta$ -D-fructofuranosylation. There is only one elegant example in  $\beta$ -D-fructofuranosylation, reported by Oscarson *et al.*<sup>17</sup> 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  $\alpha$ -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  $\beta$ -furanosyl  $\alpha$ -pyranoside **5** with 68% yield, exclusively.<sup>17a</sup>

Accordingly, we initially attempted the Oscarson's method for the synthesis of **1**. However, glycosidation of 2,3,4,6-tetra-O-benzyl-5-thio-D-glucopyranose (**6**)<sup>18</sup> 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  $\beta$ -D-fructofuranosylation method was found to be incompatible with the synthesis of **1**, we turned our attention to indirect synthesis through  $\beta$ -D-psicofuranosylation, which was employed in the stereoselective synthesis of sucrose previously.<sup>19</sup> We have reported that glycosidation of D-glucopyranose with D-psicofuranosyl donor<sup>20</sup> protecting 3,4-diols with acetonide gave  $\beta$ -D-psicofuranosyl  $\alpha$ -D-glucopyranoside, which afforded sucrose after several steps. D-Psicofuranosyl donor was regarded as  $\beta$ -D-fructofuranosyl donor in the disaccharide syntheses.<sup>19,21</sup> 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  $\alpha$ -D-fructofuranosyl  $\alpha$ -D-glucopyranoside predominantly which was used for the synthesis of isosucrose. The course of  $\alpha$ -D-fructofuranosylation or  $\beta$ -D-psicofuranosylation could be governed by the stereochemistry of the C-3 hydroxy substituent. Glycosidation of acceptor with D-fructofuranosyl donor is not sufficient for the syntheses of  $\beta$ -D-fructofuranosides, but is suitable for  $\alpha$ -D-fructofuranoside. Based on the above results, synthetic plan for **1** and **2** is depicted in Fig. 2.

D-Fructofuranosyl donor with 5-thiogluco acceptor would give  $\alpha$ -D-fructofuranosyl 5-thio- $\alpha$ -D-glucopyranoside, of which anomeric centers would matched with the stereochemistry of **2**. Glycosylation of 5-thiogluco acceptor with D-psicofuranosyl donor would give  $\beta$ -D-psicofuranosyl 5-thio- $\alpha$ -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,  $\alpha$ -glycoside on the anomeric center of 5-thiogluco acceptor 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,<sup>16a</sup> fructofuranosyl phosphite,<sup>16c</sup> 2-O-acetylfructofuranose,<sup>16e</sup> 2-thiofructofuranoside,<sup>16d</sup> and fructofuranosyl *N*-phenyltrifluoroacetimidate<sup>16f</sup> have been reported. Nevertheless,



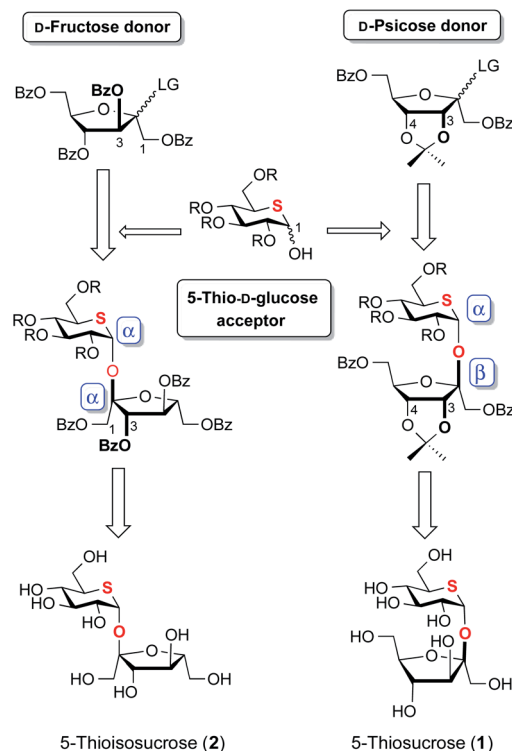
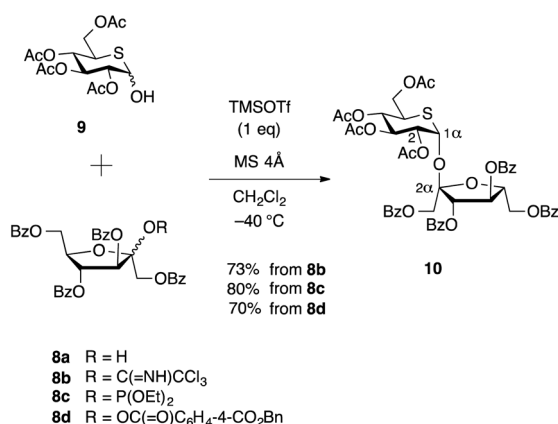


Fig. 2 Synthetic plan for 5-thiosucrose **1** and 5-thioisosucrose **2**.

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 donor<sup>22</sup> **8b**, phosphite donor **8c**,<sup>16c</sup> and benzyl phthalate donor<sup>23</sup> **8d**. These donors were prepared from 1,3,4,6-tetra-*O*-benzoyl-*D*-fructofuranose (**8a**).<sup>16b</sup> Trimethylsilyl trifluoromethanesulfonate (TMSOTf) promoted glycosylation of 2,3,4,6-tetra-*O*-acetyl-5-thio-*D*-glucose **9** (ref. 18)



Scheme 2  $\alpha$ -*D*-Fructofuranosylation of 5-thio-*D*-glucopyranose **9**.

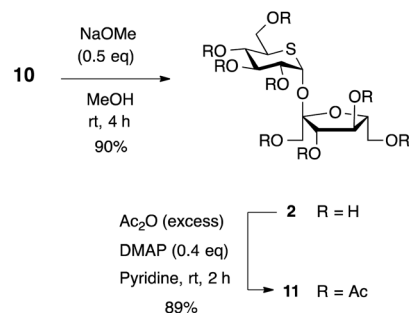
with each glycosyl donor **8b**, **8c**, or **8d**<sup>24</sup> at  $-40\text{ }^{\circ}\text{C}$  in dichloromethane in the presence of 4 Å molecular sieves resulted in the formation of 2 $\alpha$ ,1 $\alpha$ -disaccharide **10** [ $\alpha$ -*D*-Fru $\beta$ -(2 $\leftrightarrow$ 1)- $\alpha$ -*D*-Glc $\mu$ ] as a single isomer with 73%, 80%, and 70% yields, respectively. It is noteworthy that a single isomer (2 $\alpha$ ,1 $\alpha$ ) was formed exclusively among the four possible anomeric isomers (2 $\beta$ ,1 $\alpha$ , 2 $\alpha$ ,1 $\alpha$ , 2 $\alpha$ ,1 $\beta$ , and 2 $\beta$ ,1 $\beta$ ) in this glycosidation, while *D*-glucopyranosyl acceptor reported in the synthesis of isosucrose produced two anomeric isomers (2 $\alpha$ ,1 $\alpha$ , 2 $\alpha$ ,1 $\beta$ ) in moderate selectivities (47 : 53,<sup>16a</sup> 4 : 1,<sup>16c</sup> 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  $^1\text{H}$  NMR spectrum and the chemical shifts in the  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum. The  $J_{1,2}$  value of the pyranose ring proton is 3.1 Hz, which is in the typical value of  $\alpha$ -glucopyranoside, and it is identical to that of 1,2-*cis*- $\alpha$ -*D*-glucopyranoside. The  $^{13}\text{C}\{^1\text{H}\}$  NMR chemical shift of the anomeric position of the furanose ring exhibits at 109.0 ppm, which is identified to that of  $\alpha$ -*D*-fructofuranoside.<sup>17a,25</sup> 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  $\beta$ -*D*-psicofuranosidation. The initial step of this synthesis involved  $\beta$ -selective glycosylation of **6** with the *O*-protected *D*-psicofuranosyl donor **12**,<sup>18,19,24</sup> which was prepared from *D*-psicose in 49% overall yield in five steps.<sup>20b</sup> Reaction of **6** with **12** in the presence of TMSOTf in dichloromethane at  $-40$  to  $-20\text{ }^{\circ}\text{C}$  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  $\alpha$ -*D*-glucopyranoside by a  $J_{1,2}$  value of 2.9 Hz. The anomeric center in *D*-psicofuranoside was identical to  $\beta$ -



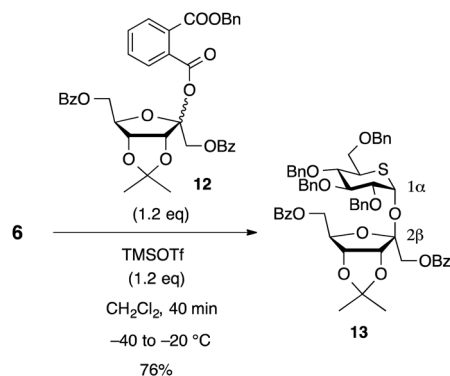
Scheme 3 Synthesis of 5-thioisosucrose **2** and its acetate **11**.



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

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

<sup>a</sup> CHCl<sub>3</sub> was used as a solvent. <sup>b</sup> Benzene-*d*<sub>6</sub> was used as a solvent. <sup>c</sup> These values were obtained from the literature.<sup>30</sup>

Scheme 4 Psicofuranosylation with 5-thio- $\alpha$ -D-glucopyranose **6**.

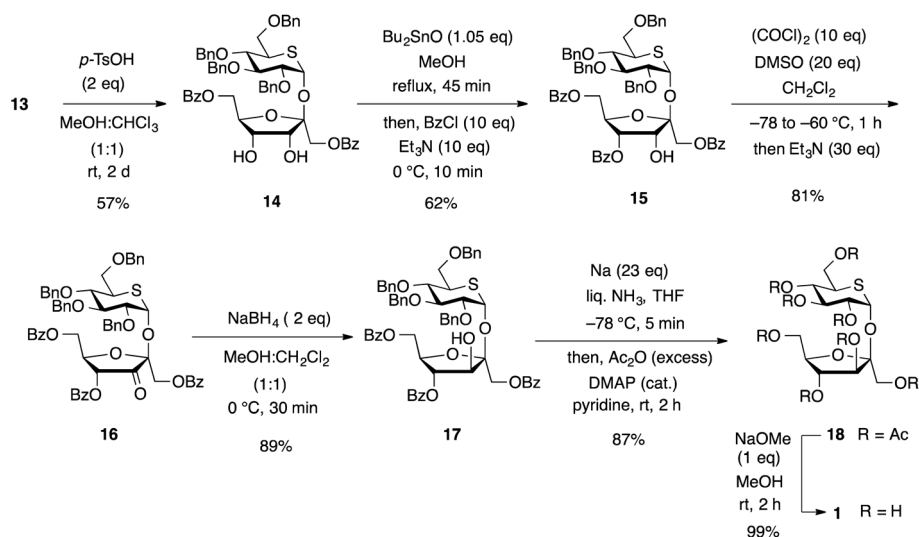
glycoside. In general, the C2-carbon of psicofuranoside appears between 107–109 ppm for  $\beta$  anomers and between 103–105 ppm for  $\alpha$  anomers,<sup>19,20</sup> and the  $^{13}\text{C}\{^1\text{H}\}$  NMR chemical shift of the anomeric carbon existed at 109.9 ppm in **13**.

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

acetonide group existing on the  $\alpha$ -side of the ring. Considering that D-psicofuranosylation of the corresponding  $\alpha$ -D-glucose gave a mixture in the ratio of 2 : 1 ( $\alpha$ -glucopyranoside vs.  $\beta$ -glucopyranoside),<sup>19</sup> 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.<sup>26</sup>

Conversion of  $\beta$ -D-psicofuranoside **13** to  $\beta$ -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 Bu<sub>2</sub>SnO in MeOH at reflux temperature followed by benzylation on the C-4 hydroxy group with benzoyl chloride gave **15** selectively.<sup>27</sup> 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 NaBH<sub>4</sub> occurred from the bottom of the furanose ring selectively to convert to  $\beta$ -D-fructofuranoside **17** in 89% yield. The direction of hydride attack in the reduction of 3-ketone is controlled by the adjacent 2- $\beta$ -glycosidic bond to give 2,3-*syn*-product.<sup>28</sup> Removal of both O-benzoyl and O-benzyl groups in disaccharide **17** under the Birch conditions and

Scheme 5 Synthesis of **1**.



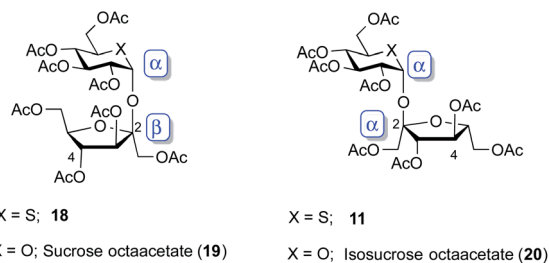


Fig. 3 Octaacetate of 5-thiosucrose **18**, 5-thioisoscrose **11**, sucrose **19**, and isosucrose **20**.

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

### Stereochemistry

The specific rotations, and chemical shifts and coupling constant of  $^1\text{H}$  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**)<sup>30</sup> 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  $\alpha,\alpha$ -anomers (**11** and **20**) and those of  $\beta,\alpha$ -anomers (**18** and **19**) are comparable in  $^1\text{H}$  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  $\alpha$ -glucosidase for compounds **1**, **2**, and 5-thio-D-glucose were examined *in vitro* using rat intestinal  $\alpha$ -glucosidase. In literature, 5-thio-D-glucose is reported to be a weak to moderate inhibitor for  $\alpha$ -glucosidase.<sup>11f,12</sup> 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  $\alpha$ -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  $\alpha$ -D-fructofuranosyl 5-thio- $\alpha$ -D-glucopyranoside **10** and  $\beta$ -D-psicofuranosyl 5-thio- $\alpha$ -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  $\alpha$ -directing glycosyl acceptor for the first time. Although neither **1** nor **2** exhibit  $\alpha$ -glucosidase inhibitory activity or sweetness, current results will aid in the design of new  $\alpha$ -glucosidase inhibitors and the synthesis of other disaccharide of thiosugar derivatives.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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