


 Cite this: *RSC Adv.*, 2020, 10, 9730

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

 Atsushi Ueda,<sup>a</sup> Jinhong Pi,<sup>a</sup> Yui Makura,<sup>b</sup> Masakazu Tanaka<sup>b</sup> and Jun'ichi Uenishi<sup>\*ac</sup>

(+)-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.

 Received 3rd February 2020  
 Accepted 28th February 2020

DOI: 10.1039/d0ra01033b

[rsc.li/rsc-advances](http://rsc.li/rsc-advances)

## 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  $\alpha$ -glucosidase and non-notable activities in inhibition against  $\alpha$ -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-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

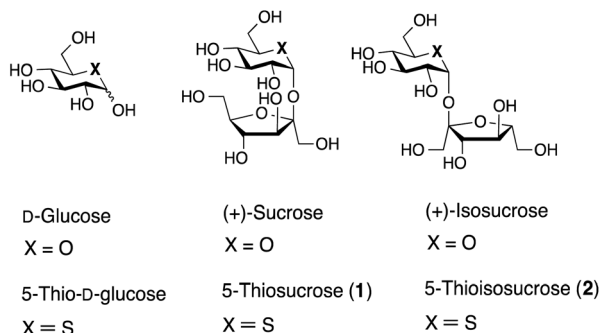


Fig. 1 Structures of glucose, sucrose, isosucrose, and their sulfur analogs.

<sup>a</sup>Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan. E-mail: [aueda@nagasaki-u.ac.jp](mailto:aueda@nagasaki-u.ac.jp); [juenishi@phs.osaka-u.ac.jp](mailto:juenishi@phs.osaka-u.ac.jp)

<sup>b</sup>Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

<sup>c</sup>Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan

† Electronic supplementary information (ESI) available: Experimental details, copies of <sup>1</sup>H, <sup>13</sup>C, and gCOSY NMR spectra. See DOI: 10.1039/d0ra01033b



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.

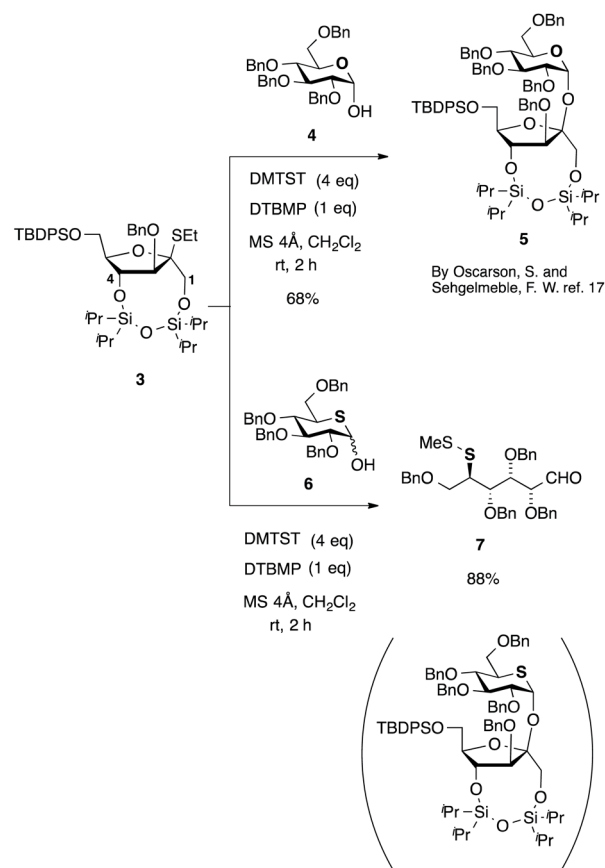
## Results and discussion

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*-Glc<sub>p</sub> and **2**;  $\alpha$ -*D*-Fruf(2 $\leftrightarrow$ 1)- $\alpha$ -*D*-Glc<sub>p</sub>] need to be controlled in a glycosylation step. An  $\alpha$ -selectivity rather than  $\beta$ -selectivity was reported for glycosylation of *D*-fructose as an either glycosyl acceptor or donor.<sup>14a</sup> In fact, glycosylation 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 glycosylation 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, glycosylation 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 glycosylation 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. Glycosylation 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-thioglucoceptor would give  $\alpha$ -*D*-fructofuranosyl 5-thio- $\alpha$ -*D*-glucopyranoside, of which anomeric centers would matched with the stereochemistry of **2**. Glycosylation of 5-thioglucoceptor 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-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,<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,



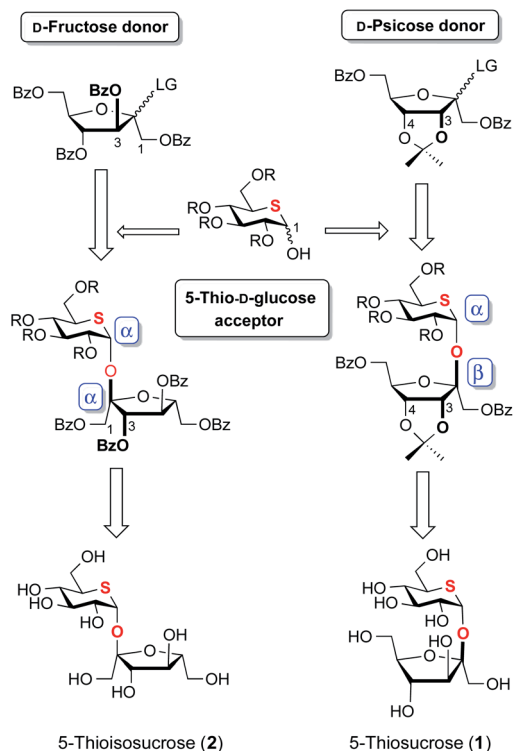
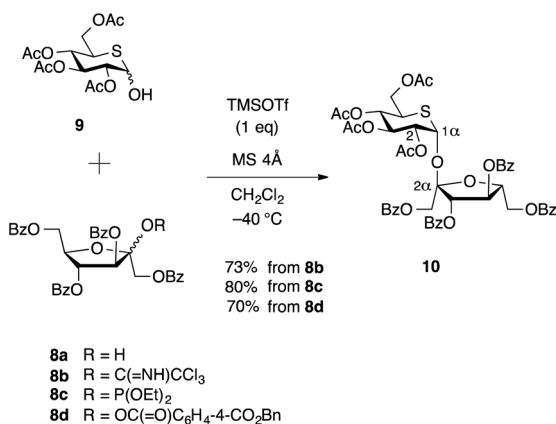


Fig. 2 Synthetic plan for 5-thiosucrose 1 and 5-thioisoscrose 2.

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 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.

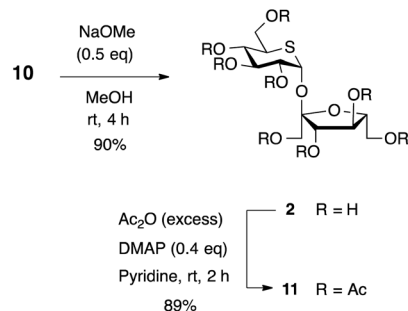
with each glycosyl donor **8b**, **8c**, or **8d**<sup>24</sup> at -40 °C in dichloromethane in the presence of 4 Å molecular sieves resulted in the formation of 2 $\alpha$ ,1 $\alpha$ -disaccharide **10** [ $\alpha$ -*D*-Fru $\alpha$ (2 $\leftrightarrow$ 1)- $\alpha$ -*D*-Glc $\beta$ ] as a single isomer 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 <sup>1</sup>H NMR spectrum and the chemical shifts in the <sup>13</sup>C{<sup>1</sup>H} NMR spectrum. The *J*<sub>1,2</sub> 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 <sup>13</sup>C{<sup>1</sup>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 glycosidation 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 °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*<sub>1,2</sub> value of 2.9 Hz. The anomeric center in *D*-psicofuranoside was identical to  $\beta$ -



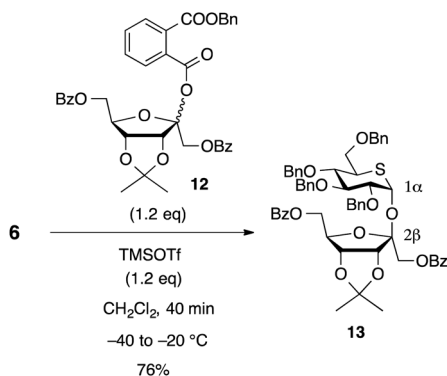
Scheme 3 Synthesis of 5-thioisoscrose 2 and its acetate 11.



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

Compound	Specific rotation <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**.

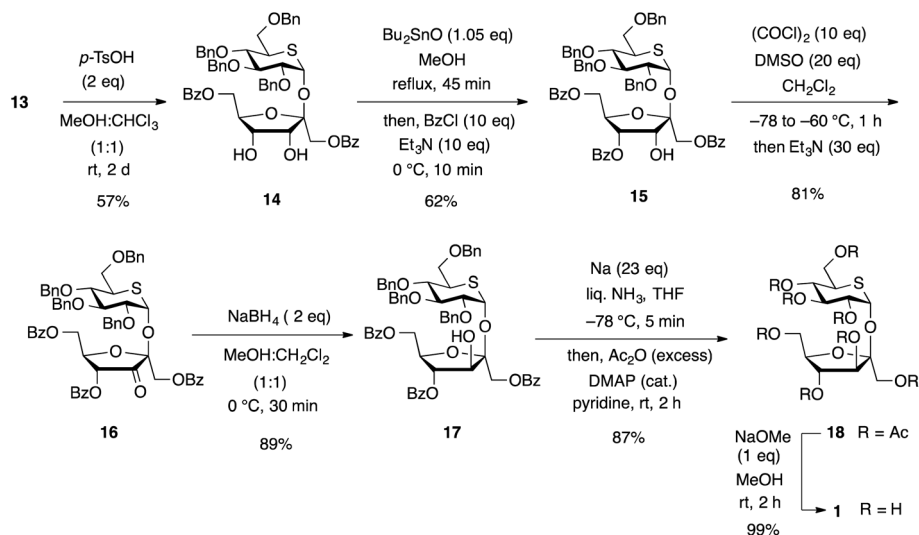
glycoside. In general, the C2-carbon of psicofuranoside appears between 107–109 ppm for  $\beta$  anomers and between 103–105 ppm for  $\alpha$  anomers,<sup>19,20</sup> and the <sup>13</sup>C{<sup>1</sup>H} NMR chemical shift of the anomeric carbon existed at 109.9 ppm in **13**.

In this reaction, protected 5-thioglucofuranose **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**.

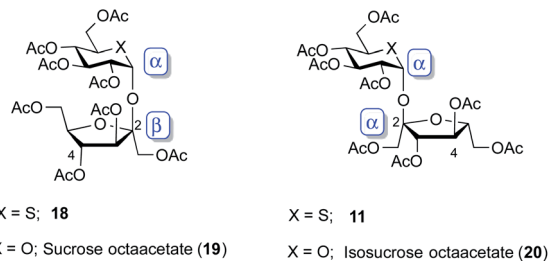


Fig. 3 Octaacetate of 5-thiosucrose **18**, 5-thioisoscrose **11**, sucrose **19**, and isosucrose **20**.

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 <sup>1</sup>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 <sup>1</sup>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

We thank professor Hisashi Matsuda and professor emeritus Masayuki Yoshikawa of Kyoto Pharmaceutical University to guide our experiments in  $\alpha$ -glucosidase assay.

## Notes and references

- (a) M. R. Jenner, Sucralose: unveiling its properties and applications, in *Progress in Sweeteners*, ed. T. H. Grenby, Elsevier Applied Science, London, U.K., 1989, pp. 121–141; (b) V. L. Grotz, S. Molinary, R. C. Peterson, M. E. Quinlan and R. Reo, Sucralose, in *Alternative Sweeteners*, ed. L. O'Brien-Nabors, CRC Press, Boca Raton, FL, 4th edn, 2006, pp. 181–196.
- (a) L. Hough and K. S. Mufti, *Carbohydr. Res.*, 1973, **29**, 291; (b) I. D. Jenkins and S. Thang, *Aust. J. Chem.*, 1984, **37**, 1925; (c) C. Simiand, E. Samain, O. R. Martin and H. Driguez, *Carbohydr. Res.*, 1995, **267**, 1; (d) F. W. Lichtenthaler and S. Mondel, *Carbohydr. Res.*, 1997, **303**, 293.
- (a) U. C. Dyer and Y. Kishi, *J. Org. Chem.*, 1988, **53**, 3383; (b) D. J. O'Leary and Y. Kishi, *J. Org. Chem.*, 1993, **58**, 304; (c) B. López-Méndez, C. Jia, Y. Zhang, L.-H. Zhang, P. Sinaÿ, J. Jiménez-Barbero and M. Sollogoub, *Chem.-Asian J.*, 2008, **3**, 51.
- R. J. Capon and J. K. MacLeod, *J. Chem. Soc., Chem. Commun.*, 1987, 1200.
- (a) M. Yoshikawa, T. Murakami, H. Shimada, H. Matsuda, J. Yamahara, G. Tanabe and O. Muraoka, *Tetrahedron Lett.*, 1997, **38**, 8367; (b) M. Yoshikawa, T. Murakami, K. Yashiro and H. Matsuda, *Chem. Pharm. Bull.*, 1998, **46**, 1339; (c) M. Yoshikawa, T. Morikawa, H. Matsuda, G. Tanabe and O. Muraoka, *Bioorg. Med. Chem.*, 2002, **10**, 1547; (d) O. Muraoka, K. Yoshikai, H. Takahashi, T. Minematsu, G. Lu, G. Tanabe, T. Wang, H. Matsuda and M. Yoshikawa, *Bioorg. Med. Chem.*, 2006, **14**, 500.
- (a) J. G. Fernandez-Bolaños, N. A. L. Al-Masoudi and I. Maya, *Adv. Carbohydr. Chem. Biochem.*, 2001, **57**, 21; (b) M. Sakono, A. Seko, Y. Takeda, M. Hachisu, A. Koizumi, K. Fujikawa, H. Seto and Y. Ito, *RSC Adv.*, 2016, **6**, 76879; 5-thiogluco-; (c) M. S. Feather and R. L. Whistler, *Tetrahedron Lett.*, 1962, **15**, 667; (d) N. A. Hughes, *J. Chem. Soc., Chem. Commun.*, 1979, 319; (e) H. Yuasa, J. Tamura and H. Hashimoto, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2763; (f) H. Driguez and



- B. Henrissat, *Tetrahedron Lett.*, 1981, **22**, 5061; (g) J. Uenishi and H. Ohmiya, *Tetrahedron*, 2003, **59**, 7011; 5-thiogalactose; (h) J. E. N. Shin and A. S. Perlin, *Carbohydr. Res.*, 1979, **76**, 165; 5-thiomannose; (i) H. Yuasa, Y. Izukawa and H. Hashimoto, *J. Carbohydr. Chem.*, 1989, **8**, 753.
- 7 (a) H. J. M. Gijzen, L. Qiao, W. Fitz and C.-H. Wong, *Chem. Rev.*, 1996, **96**, 443; (b) V. H. Lillelund, H. H. Jensen, X. Liang and M. Bols, *Chem. Rev.*, 2002, **102**, 515; 5-azaglucofuranose (nojirimycin); (c) S. Inoue, T. Tsuruoka, T. Iyo and T. Niida, *Tetrahedron*, 1968, **24**, 2125.
- 8 (a) T. Suami and S. Ogawa, *Adv. Carbohydr. Chem. Biochem.*, 1990, **48**, 21; (b) O. Arjona, A. M. Gómez, L. J. Cristóbal and J. Plumet, *Chem. Rev.*, 2007, **107**, 1919; voglibose; (c) S. Horii, H. Fukase, T. Matsuo, Y. Kameda, N. Asano and K. Matsui, *J. Med. Chem.*, 1986, **29**, 1038.
- 9 (a) S. Mehta and B. M. Pinto, *Tetrahedron Lett.*, 1992, **33**, 7675; (b) H. Yuasa, O. Hindsgaul and M. M. Palcic, *J. Am. Chem. Soc.*, 1992, **114**, 5891; (c) S. Mehta, K. L. Jordan, T. Weimar, U. C. Kreis, R. J. Batchelor, F. W. B. Winstein and B. M. Pinto, *Tetrahedron: Asymmetry*, 1994, **5**, 2367; (d) H. Hashimoto, M. Kawanishi and H. Yuasa, *Chem.-Eur. J.*, 1996, **2**, 556; (e) B. D. Johnston and B. M. Pinto, *J. Org. Chem.*, 1998, **63**, 5797; (f) Y. Morii, H. Matsuda, K. Ohara, M. Hashimoto, K. Miyairi and T. Okuno, *Bioorg. Med. Chem.*, 2005, **13**, 5113.
- 10 C.-H. Wong, Y. Ichikawa, T. Krach, C. G.-L. Narvor, D. P. Dumas and G. C. Look, *J. Am. Chem. Soc.*, 1991, **113**, 8137.
- 11 (a) D. J. Hoffman and R. L. Whistler, *Biochemistry*, 1968, **7**, 4479; (b) R. L. Whistler and W. C. Lake, *Biochem. J.*, 1972, **130**, 919; (c) B. Hellman, Å. Lernmark, J. Sehlin, I.-B. Täljedal and R. L. Whistler, *Biochem. Pharmacol.*, 1973, **22**, 29; (d) J. R. Zysk, A. A. Bushway, R. L. Whistler and W. W. Carlton, *J. Reprod. Fertil.*, 1975, **45**, 69; (e) J. H. Kim, S. H. Kim, E. W. Hahn and C. W. Song, *Science*, 1978, **200**, 206; (f) Y. L. Merrer, M. Fuzier, I. Dosbaa, M.-J. Foglietti and J.-C. Depezay, *Tetrahedron*, 1997, **53**, 16731.
- 12 T. Kajimoto, K. K.-C. Liu, R. L. Pederson, Z. Zhong, Y. Ichikawa, J. A. Porco Jr and C.-H. Wong, *J. Am. Chem. Soc.*, 1991, **113**, 6187.
- 13 (a) S. Chiba, *Biosci., Biotechnol., Biochem.*, 1997, **61**, 1233; (b) E. B. de Melo, A. S. Gomes and I. Carvalho, *Tetrahedron*, 2006, **62**, 10277.
- 14 (a) P. Fügedi, Glycosylation methods, in *The Organic Chemistry of Sugars*, ed. D. E. Levy and P. Fügedi, CRC Press, Boca Raton, FL, 2006; (b) *Handbook of Chemical Glycosylation*, ed. A. V. Demchenko, WILEY-VCH, Weinheim, Germany, 2008.
- 15 (a) R. U. Lemieux and G. Huber, *J. Am. Chem. Soc.*, 1953, **75**, 4118; (b) R. U. Lemieux and G. Huber, *J. Am. Chem. Soc.*, 1956, **78**, 4117; (c) H. Tsuchida and M. Komoto, *Agric. Biol. Chem.*, 1965, **29**, 239; (d) R. K. Ness and H. G. Fletcher Jr, *Carbohydr. Res.*, 1971, **17**, 465; (e) D. E. Iley and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1975, **97**, 2563; (f) B. Fraser-Reid and D. E. Iley, *Can. J. Chem.*, 1979, **57**, 645.
- 16 (a) A. Klemer, K. Gaupp and E. Buhe, *Tetrahedron Lett.*, 1969, **52**, 4585; (b) A. Bouali, G. Descotes, D. F. Ewing, A. Grouiller, J. Lefkidou, A.-D. Lespinasse and G. Mackenzie, *J. Carbohydr. Chem.*, 1992, **11**, 159; (c) T. Müller, R. Schneider and R. R. Schmidt, *Tetrahedron Lett.*, 1994, **35**, 4763; (d) Y.-L. Li and Y.-L. Wu, *Tetrahedron Lett.*, 1996, **37**, 7413; (e) T. Yamanoi, N. Misawa and M. Watanabe, *Tetrahedron Lett.*, 2007, **48**, 6458; (f) G. Lian, Q. Gao and F. Lin, *Carbohydr. Res.*, 2008, **343**, 2992.
- 17 (a) S. Oscarson and F. W. Sehgelmeble, *J. Am. Chem. Soc.*, 2000, **122**, 8869; (b) S. Oscarson and F. W. Sehgelmeble, *J. Org. Chem.*, 2002, **67**, 8457; (c) S. Oscarson and F. W. Sehgelmeble, *Tetrahedron: Asymmetry*, 2005, **16**, 121.
- 18 An  $\alpha$ -anomer exists predominantly ( $\alpha : \beta = >10 : 1$ ) in **6** and **9**.
- 19 J. Uenishi and A. Ueda, *Tetrahedron: Asymmetry*, 2008, **19**, 2210.
- 20 Other examples of  $\beta$ -D-psicofuranosylations; (a) J. Uenishi and A. Ueda, *Heterocycles*, 2009, **77**, 1297; (b) A. Ueda, T. Yamashita and J. Uenishi, *Carbohydr. Res.*, 2010, **345**, 1722; (c) A. Ueda, Y. Nishimura, Y. Makura, M. Tanaka and J. Uenishi, *Heterocycles*, 2018, **97**, 729.
- 21 A. Ueda, T. Yamashita and J. Uenishi, *Heterocycles*, 2010, **81**, 1711.
- 22 R. R. Schmidt and J. Michel, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 731.
- 23 K. S. Kim, Y. J. Lee, H. Y. Kim, S. S. Kang and S. Y. Kwon, *Org. Biomol. Chem.*, 2004, **2**, 2408.
- 24 A mixture of  $\alpha$ - and  $\beta$ -anomers; for **8d** ( $\alpha : \beta = 1 : 1.2$ ) and for **12** ( $\alpha : \beta = 1 : 15$ ).
- 25 S. J. Angyal and G. S. Bethell, *Aust. J. Chem.*, 1976, **29**, 1249.
- 26 The similar results were observed in the case of D-glucopyranosylation of D-fructofuranose as well as D-tagatofuranose. The glycosylation of **4** with D-fructofuranose **8c** gave a mixture of pyranosides,  $\alpha$ -D-Fruf-(2 $\leftrightarrow$ 1)- $\alpha$ -D-Glcp and  $\alpha$ -D-Fruf-(2 $\leftrightarrow$ 1)- $\beta$ -D-Glcp, in a 5 : 4 ratio. Y. Makura, A. Ueda, T. Matsuzaki, T. Minamino and M. Tanaka, *Tetrahedron*, 2019, **75**, 3758.
- 27 D. Wagner, J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 1974, **39**, 24.
- 28 (a) A. Földesi, T. V. Maltseva, Z. Dinya and J. Chattopadhyaya, *Tetrahedron*, 1998, **54**, 14487; (b) A. Földesi, A. Trifonova, Z. Dinya and J. Chattopadhyaya, *J. Org. Chem.*, 2001, **66**, 6560.
- 29 G. Zemplén and E. Pacsu, *Ber. Dtsch. Chem. Ges.*, 1929, **62**, 1613.
- 30 G. R. Newkome, J. D. Sauer, V. K. Majestic, N. S. Bhacca, H. D. Braymer and J. D. Wander, *Carbohydr. Res.*, 1976, **48**, 1.

