HETEROCYCLES, Vol. 71, No. 3, 2007, pp. 517 - 522. © The Japan Institute of Heterocyclic Chemistry
Received, 4th December, 2006, Accepted, 15th January, 2007, Published online, 15th January, 2007. COM-06-10965

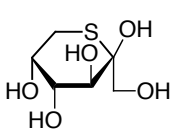
THE FIRST CHEMICAL SYNTHESIS OF 6-THIO-D-FRUCTO-PYRANOSE *VIA* METHYL 6-BROMO-6-DEOXY-1,3-*O*-ISOPRO-PYLIDENE-α-D-FRUCTOFURANOSIDE AS A KEY INTERMEDIATE

Tadashi Hanaya,* Nobuaki Sato, and Hiroshi Yamamoto[1]

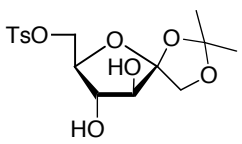
Department of Chemistry, Faculty of Science, Okayama University, Tsushima-naka, Okayama 700-8530, Japan. E-mail: hanaya@cc.okayama-u.ac.jp

Abstract – Selective bromination of sucrose, followed by acetalation with 2,2-dimethoxypropane in 1,4-dioxane in the presence of *p*-toluenesulfonic acid, afforded methyl 6-bromo-6-deoxy-1,3-*O*-isopropylidene-α-D-fructofuranoside (**4**). The first chemical synthesis of 6-thio-D-fructopyranose was accomplished from **4** through its 6-*S*-acetyl-6-thio derivative.

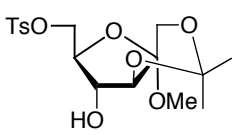
Various thiosugars containing a sulfur atom in the hemiacetal ring[2] have been synthesized because of wide interest in their chemical and biological activities. Some of them interfere with enzymes involved in the recognition of their natural counterparts; *e.g.*, 5-thio-D-glucose shows a potent, competitive inhibitor of cellular D-glucose transport,[3] whereas 5-thio-L-fructose exhibits a strong α-fructosidase inhibitory activity.[4] Thiosugar analogs of D-glucosamine and D-mannnosamine are potentially useful owing to their inhibitory activity in the biosynthesis of important constituents of higher animal cell walls.[5] Among these thiosugars, 6-thio-D-fructopyranose (**1**) has drawn interest because it shows various antiradiation properties in cells.[6] Furthermore **1** was found to be significantly sweeter than D-fructose and has been studied as for the structural and mechanistic aspects associated with sweetness.[7] Synthesis of **1**, however, has not been achieved by chemical procedures but so far only by the enzyme-catalyzed reactions such as isomerization of 6-thio-D-glucose with the aid of D-glucose isomerase[8] or condensation of 3-thioglyceraldehyde with dihydroxyacetone phosphate in the presence of rabbit muscle aldolase.[9] The use of these enzymatic procedures for synthesis of **1** is ascribed to the lack of an efficient chemical process to obtain the versatile key precursors from readily available sugar materials.



1

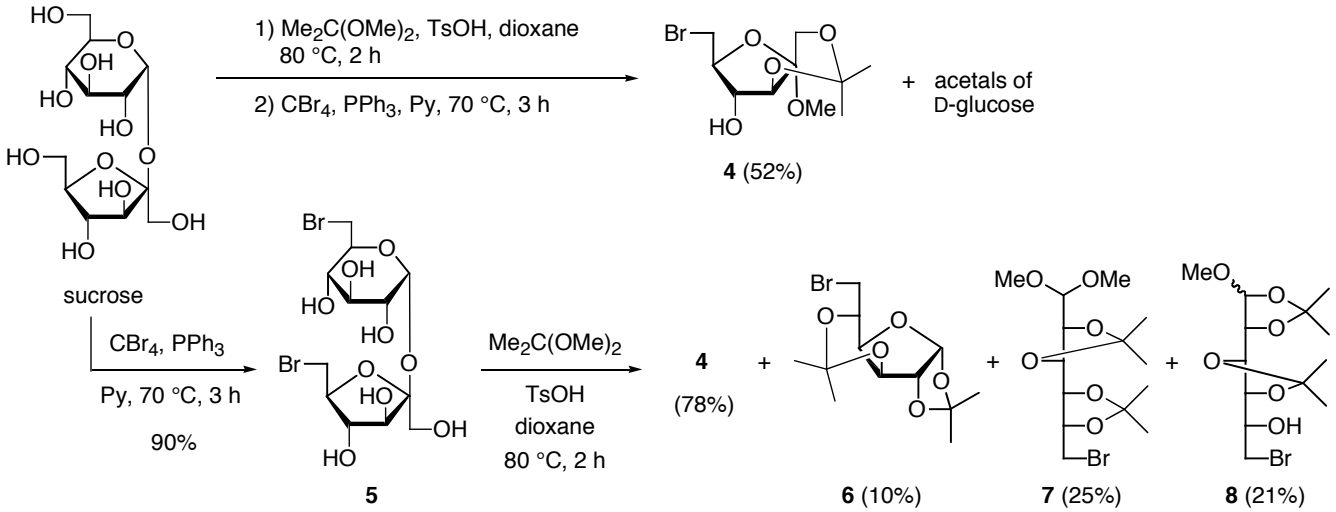


2



3

1,2-*O*-Protected D-fructofuranose derivatives having an appropriate leaving group at C-6 can be perceived as the most suitable precursors for introduction of a thio group onto the C-6 atom. However, preparation of D-fructofuranose acetals from D-fructose has been accomplished in a rather low yield in comparison with that of D-fructopyranose acetals.[10] For example, 1,2-*O*-isopropylidene-6-*O*-tosyl-β-D-fructofuranose (**2**), possibly a desirable precursor for our purpose, is obtainable by acetalation of D-fructose with 2,2-dimethoxypropane in the presence of tin chloride, followed by tosylation but its yield remains rather low (23%).[11] Meanwhile, we have recently reported efficient synthetic procedures of methyl 1,3-*O*-isopropylidene-α-D-fructofuranoside derivatives from sucrose instead of D-fructose:[12] *i.e.*, treatment of sucrose with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in 1,4-dioxane followed by tosylation afforded methyl 1,3-*O*-isopropylidene-6-*O*-tosyl-α-D-fructofuranoside (**3**) in 48% yield. Although this compound was also regarded as a useful precursor for our purpose, we have pursued a novel alternative derivative obtainable in a higher yield and describe herein the preparation of a versatile precursor for 6-*C*-substituted D-fructoses, 6-bromo-6-deoxy-D-fructofuranoside derivative (**4**), starting from readily available sucrose, together with the first chemical synthesis of 6-thio-D-fructopyranose (**1**) by use of **4** with relatively simple procedures in a high overall yield.



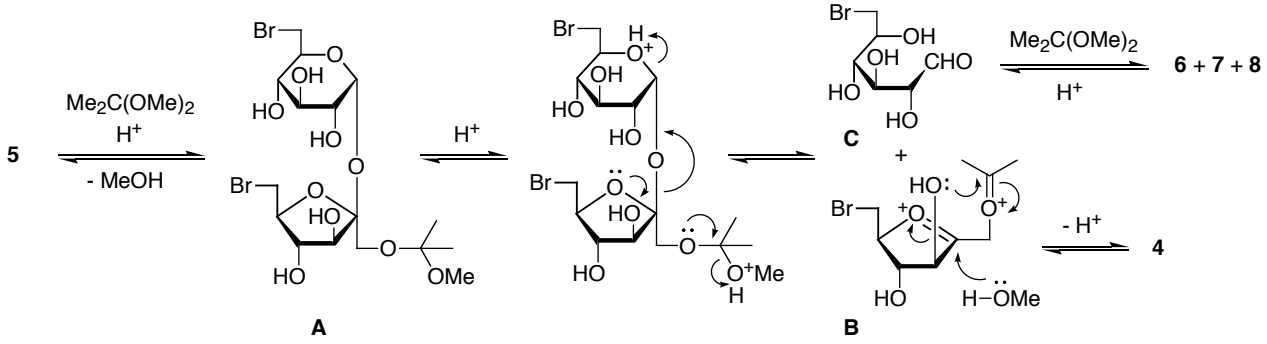
Scheme 1

For an alternative leaving group at C-6 of the D-fructofuranoside derivative, we have chosen a bromo substituent which is available for the direct replacement of primary hydroxy groups (Scheme 1). Acetalation of sucrose with 2,2-dimethoxypropane in 1,4-dioxane in the presence of *p*-toluenesulfonic acid at 80 °C afforded a mixture of acetals,[12] which was then treated with carbon tetrabromide (1.5 mol equiv.) and triphenylphosphine (3 mol equiv.) in pyridine at 70 °C to provide methyl 6-bromo-6-deoxy-1,3-*O*-isopropylidene-D-fructofuranoside (**4**) in 52% yield, together with acetals of D-glucose.[13]

As an alternative approach for the preparation of **4**, we intended to reverse the order of acetalation and

introduction of a leaving group. Tosylation of sucrose using tosyl chloride (2 mol equiv.) in pyridine has resulted in the isolation of 6,6'-di-*O*-tosylsucrose in ca. 20% yield,[14] suggesting that this reaction sequence is unsuitable for preparation of the 6-*O*-tosyl derivative (**3**). Selective bromination of sucrose with carbon tetrabromide (3 mol equiv.) and triphenylphosphine (6 mol equiv.),[15] on the other hand, turned out to afford 6,6'-dibromo-6,6'-dideoxysucrose (**5**) in 90% yield. Acetalation of **5** under the same conditions as those employed for sucrose yieled a mixture of D-fructose and D-glucose derivatives. By purification on a silica gel column chromatography the desired D-fructofuranoside derivative (**4**) was obtained as the major product (78%), along with 6-deoxy-6-bromo-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (**6**)[16] (10%), 6-bromo-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-glucose dimethyl acetal (**7**) (25%), and 6-bromo-6-deoxy-1,2:3,4-di-*O*-isopropylidene-1-methoxy-D-glucitol (**8**) (21%).[17]

A possible pathway for the formation of these acetals from **5** is illustrated in Scheme 2. The acetalation of a primary hydroxy group of **5** with 2,2-dimethoxypropane would proceed through the 1'-*O*-(1-methoxy-1-methylethyl) derivative (**A**). The cleavage of the β-fructofuranoside linkage of **A** would then afford the fructofuranosyl oxycarbonium ion (**B**) and the D-glucose moiety (**C**). The former would give rise to the D-fructofuranoside derivative (**4**) by the 1,3-*O*-acetalation and the addition of methanol to C-2, while the latter would be subjected to further reactions with 2,2-dimethoxypropane to provide acetals of D-glucofuranose (**6**) and acyclic D-glucoses (**7, 8**).[18]



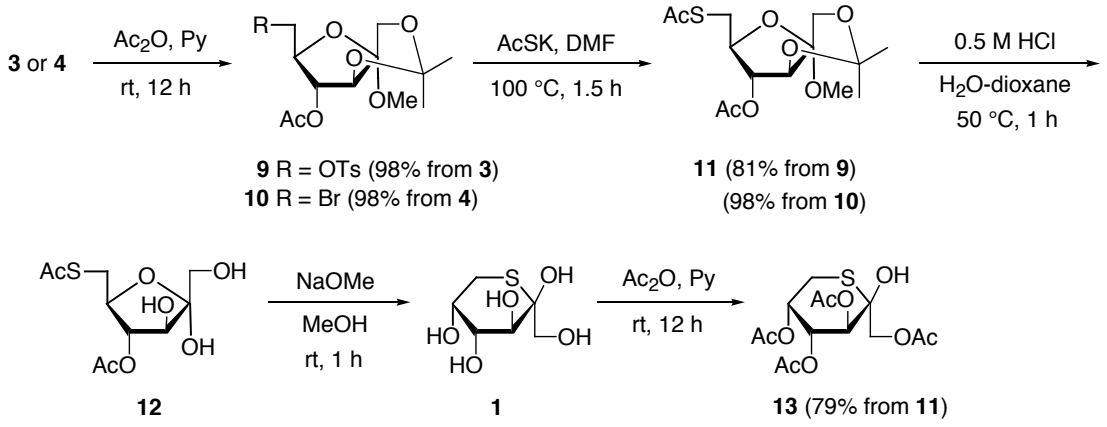
Scheme 2

This synthetic procedures can thus be perceived as the most effective pathway for the preparation of the 6-*C*-substituted D-fructofuranose derivatives. The 6-bromo-6-deoxy-D-fructofuranoside derivative (**4**), as well as the 6-*O*-tosyl compound (**3**), is regarded as a potentially useful precursor for the synthesis of D-fructose derivatives substituted at C-6, such as 6-thio-,[8,9] 6-deoxy-6-amino-,[19] and 6-deoxy-6-phosphinoyl-D-fructoses.[11,20]

An efficient preparation of 6-thio-D-fructofuranose (**1**) from **3** and **4** was achieved by the sequence illustrated in Scheme 3. Namely, the 6-*O*-tosyl and 6-bromo compounds (**3**,**4**) were acetylated with acetic anhydride-pyridine to afford the corresponding 4-*O*-acetyl derivatives (**9**,**10**), respectively. Treatment of the 6-*O*-tosylate (**9**) with potassium thioacetate in DMF at 100 °C provided the 6-*S*-acetyl-6-thio derivative (**11**) in 81%, while the same treatment of 6-bromide (**10**) afforded **11** in a

better yield (98%).

Removal of the protecting groups of **11** was carried out in the following two steps. The acetal moieties of **11** were cleaved by the action of 0.5 M hydrochloric acid at 50 °C for 1 h to afford the D-fructofuranose derivative (**12**). The acetyl groups of **12** were then removed by treatment with sodium methoxide in methanol at room temperature to provide 6-thio-β-D-fructopyranose (**1**), which was then purified and characterized as the tetraacetate (**13**)[21] (79% overall yield from **11**).



Scheme 3

Present work thus demonstrates the first chemical synthesis of D-fructopyranose thiosugar (**1**) from appropriate D-fructofuranoside derivatives (**9**,**10**). The 6-bromo-6-deoxy derivative (**10**) derived from sucrose in a satisfactory yield can be regarded as a highly useful precursor for C-6 substituted D-fructose derivatives.

ACKNOWLEDGEMENTS

We are grateful to the SC-NMR Laboratory of Okayama University for the NMR measurements.

REFERENCES AND NOTES

1. Present address: School of Pharmacy, Shujitsu University, Okayama 703-8516, Japan.
2. R. L. Whistler and W. C. Lake, *Methods Carbohydr. Chem.,* 1972, **6**, 286; M. J. Pitts, M. Chmielewski, M. S. Chen, M. M. A. Abd El-Rahman, and R. L. Whistler, *Arch. Biochem. Biophys.,* 1975, **169**, 384; R. J. Capon and K. MacLead, *J. Chem. Soc., Chem. Commun*., 1987, 1200; H. Yuasa, M. Izumi, and H. Hashimoto, *Yuki Gosei Kagaku Kyokai Shi*, 2002, **60**, 774.
3. B. Hellman, A. Lernmark, J. Sehlin, I.-B. Taljedal, and R. L. Whistler, *Biochem. Pharmacol*., 1973, **22**, 29; M. Chen and R. L. Whistler, *Arch. Biochem. Biophys*., 1975, **169**, 392.
4. H. Hashimoto, T. Fujimori, and H. Yuasa, *J. Carbohydr. Chem*., 1990, **9**, 683.
5. P. K. Ray, *Adv. Appl. Microbiol*., 1971, **21**, 227.

6. R. L. Whistler, *U. S. Patent,* 4,420,489, 1983; *Chem. Abstr*., 1984, **100**, P117256n.
7. M. G. Lindley, R. S. Shallenberger, and R. L. Whistler, *J. Food Sci*., 1976, **41**, 575; R. J. Woods, V. H. Smith Jr., W. A. Szarek, and A. Farazdel, *J. Chem. Soc., Chem. Commn*., 1987, 937.
8. M. Chmielewski, M.-S. Chen, and R. L. Whistler, *Carbohydr. Res*., 1976, **49**, 479.
9. F. Effenberger, A. Straub, and V. Null, *Liebigs Ann. Chem.,* 1992, 1297; W.-C. Chou, L. Chen, J.-M. Fang, and C.-H. Wong, *J. Am. Chem. Soc*., 1994, **116**, 6191.
10. G. J. F. Chittenden, *J. Chem. Soc., Chem. Commun.*, 1980, 882; E. Fanton, J. Gelas, and D. Horton, *J. Chem. Soc., Chem. Commun.*, 1980, 21; R. F. Brady Jr., *Carbohydr. Res.*, 1970, **15**, 35.
11. T. Hanaya, R. Okamoto, Y. V. Prikhod'ko, M.-A. Armour, A. M. Hogg, and H. Yamamoto, *J. Chem. Soc. Perkin Trans. 1*, 1993, 1663.
12. T. Hanaya, N. Sato, and H. Yamamoto, *Carbohydr. Res*., 2005, **340**, 2494.
13. The resulting D-glucose acetals underwent no bromination, because their primary hydroxy groups were protected by isopropylidene groups (see, Ref. 12).
14. C. H. Bolton, L. Hough, and R. Khan, *Carbohydr. Res*., 1972, **21**, 133; R. U. Lemieux and J. P. Barrette, *Can. J. Chem*., 1960, **38**, 656.
15. A. K. M. Anisuzzaman and R. L. Whistler, *Carbohydr. Res*., 1978, **61**, 511; L. Hough, L. V. Sinchareonkul, and A. C. Richardson, *Carbohydr. Res*., 1988, **174**, 145.
16. S. Hanessian, M. M. Ponpipom, and P. Lavallee, *Carbohydr. Res*., 1972, **24**, 45.
17. **Acetalation of 5.** To a solution of **5** (680 mg, 1.45 mmol) in dry dioxane (10 mL) were added 2,2-dimethoxypropane (2.5 mL, 20 mmol) and *p*-toluenesulfonic acid monohydrate (40 mg, 0.21 mmol). The mixture was stirred at 80 °C for 2 h, neutralized with pyridine at rt, and then concentrated in vacuo. The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was separated by silica-gel column chromatography with a gradient eluent of 1:7 to 1:3 AcOEt-hexane to give compounds **6–8** and **4**.
6: Colorless syrup (47.0 mg, 10% yield); R_f = 0.63 (1:3 AcOEt-hexane). **7**: Colorless syrup (134 mg, 25%); R_f = 0.54; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.37, 1.40, 1.42, 1.50 (3H each, 4s, CMe_2), 3.43, 3.44 (3H each, 2s, MeO-1), 3.63 (1H, dd, $J_{6,6'}$ = 10.3, $J_{5,6'}$ = 7.3 Hz, H'-6), 3.65 (1H, dd, $J_{5,6}$ = 6.4 Hz, H-6), 4.02 (1H, d, $J_{2,3}$ = 8.0, $J_{3,4}$ = 1.5 Hz, H-3), 4.11 (1H, dd, $J_{1,2}$ = 5.9 Hz, H-2), 4.30 (1H, dd, $J_{4,5}$ = 6.8 Hz, H-4), 4.39 (1H, d, H-1), 4.50 (1H, ddd, H-5). **8**: Colorless syrup (108 mg, 21%); R_f = 0.43; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.39, 1.43, 1.50, 1.50 (3H each, 4s, CMe_2), 3.30 (1H, br s, HO-5), 3.41 (3H, s, MeO-1), 3.54 (1H, dd, $J_{6,6'}$ = 11.0, $J_{5,6'}$ = 7.3 Hz, H'-6), 3.745 (1H, dd, $J_{5,6}$ = 2.6 Hz, H-6), 3.76 (1H, td, $J_{4,5}$ = 7.9 Hz, H-5), 3.91 (1H, dd, $J_{3,4}$ = 6.6 Hz, H-4), 4.20 (1H, dd, $J_{2,3}$ = 3.8 Hz, H-3), 4.22 (1H, dd, $J_{1,2}$ = 3.0 Hz, H-2), 5.08 (1H, d, H-1). **4**: Colorless syrup (336 mg, 78%); R_f = 0.24; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.37, 1.45 (3H each, 2s, CMe_2), 2.44 (1H, br s, HO-4), 3.32 (3H, s, MeO-2), 3.48 (1H, dd, $J_{6,6'}$ = 10.0, $J_{5,6'}$ = 8.2 Hz, H'-6), 3.53 (1H, dd, $J_{5,6}$ = 6.1 Hz, H-6), 3.90, 3.96 (1H each, 2d, $J_{1,1'}$ = 12.2 Hz, H,H'-1), 4.02 (1H, d, $J_{4,5}$ = 2.0, $J_{3,4}$ = 0 Hz, H-4), 4.05 (1H, s, H-3), 4.26 (1H, ddd, H-5).
18. The absence of D-glucopyranose acetonides is ascribed to the lack of 6-hydroxy group. The predominant formation of acyclic D-glucose acetonides has also been observed in acetalation of

D-glucose under the same conditions (see, Ref. 12).

19. P. Page, C. Blonski, and J. Périé, *Tetrahedron*, 1996, **52**, 1557.
20. T. Hanaya, K. Imai, Y. V. Prikhod'ko, and H. Yamamoto, *Carbohydr. Res*., 2005, **340**, 31.
21. Compound (**13**): mp 154–155 °C (Ref. 8, mp 155–156 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.00, 2.09, 2.14, 2.17 (3H each, 4s, AcO-1,3,4,5), 2.20 (1H, br s, HO-2), 2.78 (1H, dd, $J_{6,6'}$ = 14.7, $J_{5,6'}$ = 4.4 Hz, H'-6), 3.32 (1H, dd, $J_{5,6}$ = 1.7 Hz, H-6), 4.21, 4.27 (1H each, 2d, $J_{1,1'}$ = 12.0 Hz, H,H'-1), 5.38 (1H, dd $J_{3,4}$ = 10.3, $J_{4,5}$ = 3.2 Hz, H-4), 5.50 (1H, ddd, H-5), 5.62 (1H, d , H-3).