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An efficient synthesis of methyl 1,3-*O*-isopropylidene-α-D-fructofuranoside and 2,3:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal derivatives from sucrose

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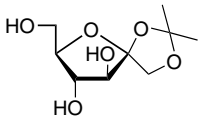
Abstract—Acetalation of sucrose with 2,2-dimethoxypropane in 1,4-dioxane in the presence of *p*-toluenesulfonic acid, followed by acetylation, afforded methyl 4,6-di-*O*-acetyl-1,3-*O*-isopropylidene-α-D-fructofuranoside and 4-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal as major products, while tosylation of the intermediate acetals provided methyl 6-*O*-tosyl-1,3-*O*-isopropylidene-α-D-fructofuranose.

Keywords: Acetalation of sucrose; D-Fructofuranoside; D-Glucose dimethyl acetal; Isopropylidene acetal

1. Introduction

Acetonation (isopropylidenation) is the most widely used reaction for the initial step of carbohydrate derivatization and many methods are known to accomplish this reaction.[1] Acetal exchange using 2,2-dimethoxypropane[2,3] or 2-methoxypropene[4,5] in the presence of acid catalyst is frequently used for introducing an isopropylidene group, and affords different products from those by the direct acetalation using acetone. For example, acetal exchange of D-fructose with 2,2-dimethoxypropane and 2-methoxypropene provides 1,2-*O*-isopropylidene-β- (**1**)[3] and 1,3-*O*-isopropylidene-α-D-fructofuranose (**2**),[5] respectively, whereas acetalation of D-fructose with acetone affords 1,2:4,5- and 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranoses.[6] Among these acetals, the D-fructofuranoses, whose primary hydroxy group at C-1 and an anomeric hydroxy group are protected, can be perceived as starting materials for the synthesis of D-fructose derivatives substituted at C-6: such as 6-deoxy-6-azido-,[7,8] 6-deoxy-6-amino-,[8] 6-thio-,[9,10] and 6-deoxy-6-phosphinoyl-D-fructoses.[8,11,12] Although these 6-*C*-substituted derivatives have attracted considerable interest as precursors for imino-,[8] thio-,[9,13] and phospho-sugar analogs[11,12] of D-fructopyranose, most of them have been prepared by the use of enzymatic procedures with D-fructose 1,6-diphosphate aldolase[7–9] so far, because of the lack of efficient chemical procedures for the suitable starting materials.



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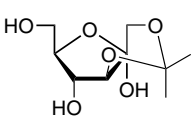

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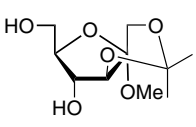

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As for D-fructofuranoses, the formation of **1** proceeds in a low yield (28% as the corresponding triacetate) and **2** is needed further glycosidation for protection of the anomeric OH group.[12] Meanwhile, Richardson and co-workers obtained the diacetate of methyl 1,3-*O*-isopropylidene-α-D-fructofuranoside (**3**) in 36% yield from sucrose by the use of 2,2-dimethoxypropane and *p*-toluenesulfonic acid in DMF followed by acetylation,

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Table 1. Acetalation and subsequent acetylation of sucrose, D-glucose, and D-fructose

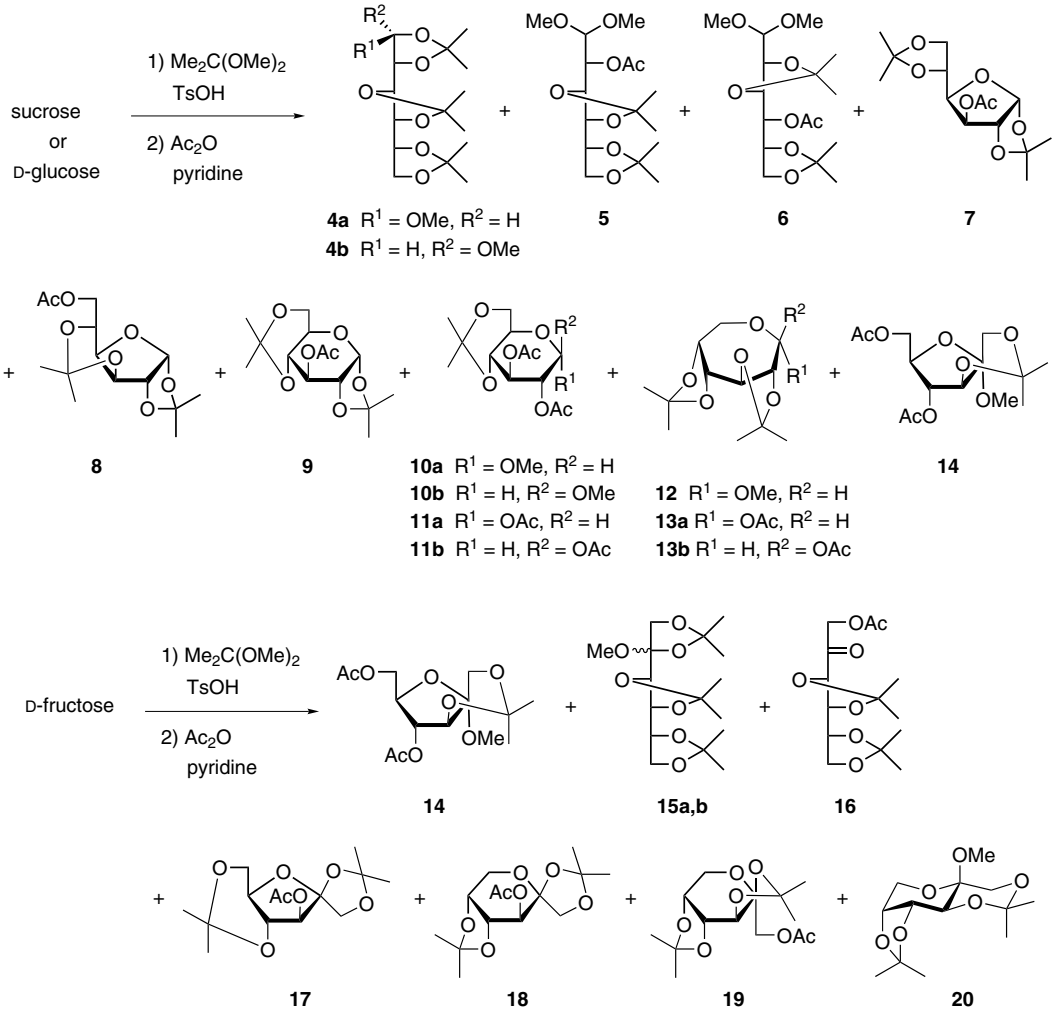
Entry	Substrate	Reaction condition of acetalation[a]	Yields (%) of D-glucose derivatives	Yields (%) of D-fructose derivatives
1[b]	Sucrose	DMF, rt, 36 h	**4a** (6.0), **7** (12.5), **9** (9.1), **11a**,**b** (16)	**14** (36)
2	Sucrose	1,4-Dioxane, 80 °C, 2 h	**4a** (5.0), **4b** (1.3), **5** (9.8), **6** (49), **7** (4.8), **8** (0.7), **9** (2.1), **10a** (3.5), **10b** (2.9), **12** (1.7), **13a** (0.7)	**14** (68)
3	Sucrose	DME, 80 °C, 4 h	**4a** (6.5), **4b** (1.3), **5** (16), **6** (44), **7** (8.0), **8** (0.6), **9** (1.0), **10a** (4.7), **10b** (4.0), **12** (2.2), **13a** (0.8)	**14** (54)
4	D-Glucose	1,4-Dioxane, 80 °C, 2 h	**4a** (8.1), **4b** (4.9), **5** (6.9), **6** (41), **7** (17), **8** (2.0), **9** (3.4), **12** (0.7), **13a** (1.2), **13b** (3.6)	
5	D-Fructose	1,4-Dioxane, 80 °C, 2 h		**14** (6.9), **15a**,**b** (10), **16** (5.7), **17** (2.9), **18** (36), **19** (2.4), **20** (4.8)

[a] Catalytic amount of TsOH (0.3–0.4% w/v, 0.15 equiv) was used.
[b] Ref. 14.

together with D-glucose acetals (Table 1, entry 1).[14] As this compound was perceived as the most suitable for our purposes, we attempted to modify the reaction conditions to give **3** in satisfactory yield. We now describe an improved procedure for compound **3** by treatment of sucrose with 2,2-dimethoxypropane in 1,4-dioxane solution (Scheme 1).

2. Results and discussion

Treatment of sucrose with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in 1,4-dioxane at 80 °C for 2 h afforded a mixture of D-glucose and D-fructose derivatives (Table 1, entry 2). These products were separated, after having been converted into the corresponding



Scheme 1.

acetates by treatment with acetic anhydride–pyridine. By purification on a silica gel column, the crude products were separated into six fractions A–F, according to the order of elution. The structures and the ratios of all components in each fraction were determined on the basis of their 600 MHz ^{1}H NMR spectra (see later).

From the first-eluting fraction A, (1*S*)-1,2:3,4:5,6-tri-*O*-isopropylidene-1-methoxy-D-glucitol (**4a**)[14,15] was obtained in 5.0% yield (from sucrose), whereas methyl 2,3;4,5-di-*O*-isopropylidene-α-D-glucoseptanoside (**12**)[16] was obtained in 1.7% yield from the next fraction (B).

The third fraction (C) gave an inseparable mixture of (1*R*)-1,2:3,4:5,6-tri-*O*-isopropylidene-1-methoxy-D-glucitol (**4b**)[15] (1.3%), 6-*O*-acetyl-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (**8**)[16,17] (0.7%), and 1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-α-D-glucoseptanose (**13a**)[17] (0.7%).

The fourth fraction (D) gave an inseparable mixture of 2-*O*-acetyl-3,4:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal (**5**) (9.8%), 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**)[14,18] (4.8%), and 3-*O*-acetyl-1,2:4,6-di-*O*-isopropylidene-α-D-glucopyranose (**9**)[14] (2.1%).

The next fraction (E) gave 4-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal (**6**) in 49% yield, together with methyl 2,3-di-*O*-acetyl-4,6-*O*-isopropylidene-α-D-glucopyranoside (**10a**)[19] (3.5%) and its β anomer (**10b**)[19] (2.9%). No 1,2,3-tri-*O*-acetyl-4,6-*O*-isopropylidene-α,β-D-glucopyranoses (**11a**,**b**)[14] given in entry 1 were detected in this fraction. Compound **6** was isolated by further column chromatography of this fraction.

From the slowest-eluting fraction (F), the desired methyl 4,6-di-*O*-acetyl-1,3-*O*-isopropylidene-α-D-fructofuranoside (**14**)[14] was obtained in 68% yield, and it was a major product as well as the sole D-fructose derivative of this reaction.

The acetalation of sucrose by the use of 1,2-dimethoxyethane (DME) as a solvent required a longer reaction time as compared with 1,4-dioxane (entry 3). The resulting components are similar to those of entry 2, with a slightly lower yield of **14**.

We examined the acetalation and subsequent acetylation of both D-glucose and D-fructose under the same conditions as those of entry 2. The conversion of D-glucose resulted in the similar formation of D-glucose derivatives with those from sucrose, except for the formation of 1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-β-D-glucoseptanose (**13b**)[16] and the absence of methyl D-glucopyranosides (**10a**,**b**) (entry 4).

On the other hand, the conversion of D-fructose afforded the methyl furanoside (**14**) as a minor component (in 6.9% yield), together with a number of other products. As for the cyclic D-fructose derivatives, 3-*O*-acetyl-1,2:4;5-di-*O*-isopropylidene-β-D-fructopyranose (**18**)[20,21] was obtained as a major product (36% yield), along with 3-*O*-acetyl-1,2:4;6-di-*O*-isopropylidene-β-D-fructofuranose (**17**) (2.9%), 1-*O*-acetyl-2,3:4;5-di-*O*-isopropylidene-β-D-fructopyranose (**19**)[20] (2.4%), and methyl 1,3:4,5-di-*O*-isopropylidene-β-D-fructopyranoside (**20**) (4.8%). As acyclic D-fructose derivatives, (2*R*)- and (2*S*)-1,2:3,4:5,6-tri-*O*-isopropylidene-2-methoxy-D-glucitol (**15a**,**b**) (10%) and 1-*O*-acetyl-3,4:5,6-di-*O*-isopropylidene-D-fructose (**16**) (5.7%) were obtained.

These results support the mechanism proposed by Richardson and co-workers,[14] namely, that acetalation of primary hydroxy groups of sucrose with 2,2-dimethoxypropane takes place at first to afford the 1,1′,6′-tri-*O*-(1-methoxy-1-methylethyl) derivative. Next, the cleavage of the linkage between D-glucose and D-fructose brings about the formation of the fructofuranosyl oxycarbonium ion, which gives rise to the D-fructofuranoside (**3**) by the formation of the 1,3-*O*-isopropylidene acetal and addition of a methoxy group to C-2. The 6-*O*-(1-methoxy-1-methylethyl) group of D-fructose cleaves without cyclization, but that of D-glucose effectively affords the 5,6-*O*-isopropylidene derivatives (precursors of compounds **4**–**7**). It is noteworthy that the ratio of acyclic D-glucose derivatives (**4**–**6**) to furanoses and pyranoses is very high in entries 2 and 3. Such a tendency has been observed in acetalation of D-xylose and 2-acetamido-2-deoxy-D-glucose with 2,2-dimethoxypropane in dioxane.[22]

The precise ^{1}H NMR parameters for D-glucose and D-fructose acetals **4**–**10**, **12**–**20** are summarized in Tables 2 and 3.[†] Since compounds **5**, **6**, **15**, **16**, **17**, and **20** were obtained for the first time in the present study, structural assignments of them are discussed here in detail.

The NMR spectra of D-glucose acetals **5** and **6** revealed the presence of two methoxy groups, two isopropylidene groups, and one acetyl group. The lowest-field resonance of **5** was the H-2 signal (dd) at δ 5.15 and that of **6** was the H-4 signal (dd) at δ 5.21. These data for **5** and **6** were consistent with the structures for 2-*O*-acetyl-3,4:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal and its 4-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene analog, respectively.

The NMR spectrum of an inseparable mixture of D-fructose acetals **15a**,**b** indicated a set of C-2 epimers for tri-*O*-isopropylidene monomethyl acetal. The values (8.3–9.7 Hz) of the geminal couplings $J_{1,1'}$ and $J_{6,6'}$ for **15a**,**b** suggested that each of their C-1 and C-6 was included in a dioxolane ring (namely, $^2J_{CH_2} = 8.3$–9.3 Hz in the dioxolane ring of **4**–**7** and **18** versus $^2J_{CH_2} = 10.8$–12.2 Hz in the dioxane ring of **9**, **10**, and **14**). These facts show that **15a**,**b** have the structure of 1,2:3,4:5,6-tri-*O*-isopropylidene-D-fructose monomethyl

[†] The data for the reported compounds (**4**, **7**–**10**, **12**–**14**, **18**, and **19**) are also listed, because no complete assignments for **4**, **8**, **13**, **14**, **18**, and **19** were available in the previous reports[14–17,20] or the measurement for **7**, **9**, **10**, and **12** was done in different solvents (benzene-d_6 or acetone-d_6).[14,16,19]

Table 2. ^{1}H NMR parameters for D-glucose derivatives (**4**–**13**) in $CDCl_3$

Compound	Chemical shifts/δ									
	H-1	H-2	H-3	H-4	H-5	H-6	H′-6	MeO	AcO	Me_2C
4a	5.09	4.15	4.06	3.93	4.06	4.12	3.95	3.41	—	1.48, 1.475, 1.42, 1.41, 1.38, 1.33
4b	4.97	4.02	4.11	3.83	4.12	4.08	3.96	3.34	—	1.53, 1.44, 1.42, 1.415, 1.41, 1.36
5	4.52	5.15	4.26	3.64	4.05	4.10	3.92	3.42, 3.33	2.11	1.40, 1.39, 1.37, 1.31
6	4.34	3.83	4.20	5.21	4.27	3.99	3.90	3.415, 3.41	2.12	1.41, 1.39, 1.38, 1.34
7	5.99	4.57	4.22	4.32	3.76	4.29	4.15	—	2.08	1.49, 1.37, 1.35, 1.32
8	5.86	4.48	5.23	4.185	4.20	4.06	4.00	—	2.09	1.50, 1.39, 1.31, 1.29
9	5.52	4.04	5.08	3.695	3.81	3.95	3.69	—	2.10	1.57, 1.455, 1.37, 1.34
10a	4.87	4.84	5.37	3.67	3.725	3.89	3.74	3.37	2.06, 2.035	1.46, 1.37
10b	4.43	4.91	5.11	3.71	3.33	3.95	3.78	3.48	2.04, 2.03	1.46, 1.37
12	4.88	3.64	4.48	4.32[a]	4.28	3.73	3.41[a]	3.45	—	1.46, 1.45, 1.44, 1.36
13a	6.29	3.76	4.485	4.37	4.31	3.76	3.51	—	2.16	1.47, 1.45, 1.41, 1.35
13b	5.76	3.77	4.14	4.25	4.25	4.01	3.80	—	2.14	1.52, 1.44, 1.42, 1.36

	Coupling constants/Hz						
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
4a	3.2	3.9	7.3	8.5	6.1	4.9	8.6
4b	3.4	8.3	7.6	6.6	6.3	6.6	8.3
5	7.8	2.0	7.3	7.8	6.4	4.9	8.6
6	6.1	7.6	2.0	5.9	6.3	5.9	8.8
7	3.7	0	2.7	8.1	5.6	4.6	8.5
8	3.7	0	3.9	7.3	3.2	6.9	12.0
9	4.6	4.2	8.6	9.9	5.4	10.2	10.8
10a	3.7	9.8	9.3	9.7	5.6	10.2	11.0
10b	7.8	9.3	9.5	9.5	5.4	10.2	11.0
12	2.7	9.8	7.6	7.3	10.5	3.7	12.8
13a	2.7	9.8	7.8	7.8	10.8	3.4	13.2
13b	7.6	9.8	8.1	—	2.7	5.4	13.9

[a] $J_{4,6'}$ 1.0 Hz.

Table 3. ^{1}H NMR parameters for D-fructose derivatives (**14**–**19**) in $CDCl_3$

Compound	Chemical shifts/δ									
	H-1	H′-1	H-3	H-4	H-5	H-6	H′-6	MeO-2	AcO	Me_2C
14	3.91	3.89	4.07	4.86	4.15	4.42	4.27	3.29	2.095, 2.09	1.38, 1.43
15a[a]	4.105	3.98	4.01	4.18	4.26	4.035	3.98	3.385[b]	—	1.56, 1.435, 1.425, 1.41, 1.40, 1.36[c]
15b[a]	4.13	4.04	4.07	4.10	4.275	4.045	3.99	3.36[b]	—	1.54, 1.435, 1.43, 1.40, 1.39, 1.355[c]
16	5.05	4.92	4.46	4.25	4.19	4.10	3.96	—	2.16	1.46, 1.42, 1.39, 1.34
17	4.00	3.95	5.31	4.05	4.33	4.00	3.88	—	2.13	1.54, 1.48, 1.36, 1.34
18	3.94	3.83	5.11	4.28	4.22	4.13	4.09	—	2.13	1.55, 1.48, 1.39, 1.35
19	4.41	4.18	4.30	4.60	4.23	3.90	3.76	—	2.10	1.54, 1.48, 1.40, 1.34
20	3.93	3.60	3.88	4.27	4.29	4.01	3.90	3.31	—	1.55, 1.52, 1.49, 1.36

	Coupling constants/Hz					
	$J_{1,1'}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
14	12.2	0.7	3.9	3.9	6.6	11.7
15a	9.7	6.8	5.4	6.6	6.8	8.3
15b	9.5	6.6	4.9	6.4	6.4	8.3
16	17.8	5.9	6.6	6.3	5.1	8.8
17	9.0	6.6	6.0	7.1	5.9	12.5
18	9.3	8.1	5.4	2.7	0.7	13.4
19	11.7	2.7	7.8	2.0	0.7	12.9
20	12.7	7.8	5.6	1.3	3.2	13.2

[a] C-2 epimers: the correlation of coupled protons was confirmed by 2D-COSY measurements.
[b,c] The assignment of methoxy and isopropylidene signals may be interchanged.

acetal, although the anomeric configurations of them are still ambiguous.

The NMR spectra of D-fructose derivatives **16** and **17** indicated the presence of two isopropylidene groups and

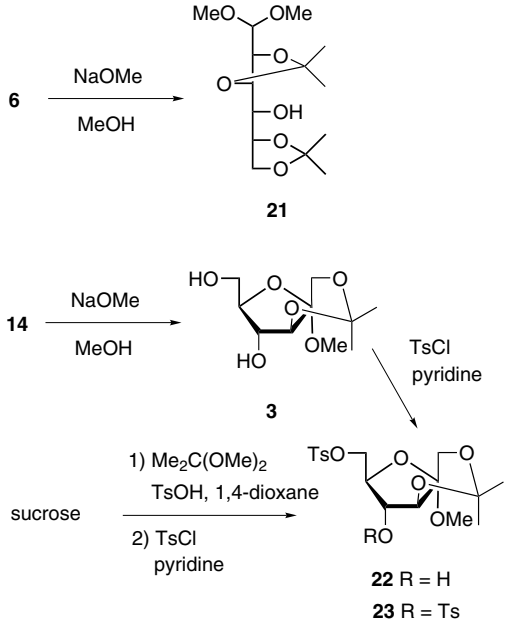
one acetyl group. The acyclic structure having 1-*O*-acetyl-3,4:5,6-di-*O*-isopropylidene unit for **16** was derived from the appearance of H_2-1 signals at a lower field (δ 5.05 and 4.92) and the magnitude of the $J_{6,6'}$ value (8.8 Hz), whereas the furanose structure having 3-*O*-acetyl-1,2:4,6-di-*O*-isopropylidene unit for **17** was assigned from the appearance of the H-3 signal at a lower field (δ 5.31), and the magnitude of the $J_{1,1'}$ (9.0 Hz) and $J_{6,6'}$ values (12.5 Hz).

The NMR spectrum of the D-fructose derivative **20** indicated the presence of two isopropylidene groups and one methyl group. The magnitude of $J_{1,1'}$ value (12.7 Hz) suggested a six-membered isopropylidene ring, whereas the resemblance of other coupling constants of **20** with those of **18** suggested the pyranose structure having the $^2C_5$ conformation. The anomeric configuration of **20** is likely to be beta, based on the nature of the fused-ring system and anomeric effect, thus indicating that compound **20** is methyl 1,3:4,5-di-*O*-isopropylidene-β-D-fructopyranoside.

Two major products **14** (68% yield from sucrose) and **6** (49%) of the present work were, respectively, converted into de-*O*-acetylated compounds **3**[14] and **21**[15,23] by treatment with sodium methoxide in methanol in almost quantitative yield (Scheme 2). The D-glucose acetal (**21**) fully protected except for 4-OH is also an important substrate, similar to **3**, for conversion into various compounds. No convenient synthesis of **21** has been reported, to the best of our knowledge, although the 4-*O*-benzoyl derivative of **21** was prepared by Curtis and Jones (~40% yield from D-glucose dimethyl dithioacetal)[23] and Stevens (34% yield from D-glucose).[15b]

As an extension of this work, the D-fructofuranoside (**3**) was converted into the 6-*O*-tosyl derivative (**22**), which is an important precursor for introducing various substituents at C-6. Thus, treatment of **3** with 1.2 equiv of tosyl chloride in pyridine afforded **22** (84%) together with a small amount of the 4,6-di-*O*-tosyl compound (**23**) (5%). As an alternative route for preparation of **22**, acetalation of sucrose, followed by direct tosylation was attempted. The mixture obtained by using the same conditions of acetalation as used in entry 2 in Table 1 was treated with 1.0 equiv of tosyl chloride to give **22** (48% from sucrose). The D-glucose acetals were difficult to tosylate owing to the absence of free primary hydroxy groups. The monotosylate **22** was easily separated from the mixture of D-glucose derivatives by column chromatography. The use of an excess (1.5 equiv) of tosyl chloride resulted in the formation of ditosylate **23** (13%) and a lower yield of **22** (39%).

In conclusion, we have developed an efficient procedure for the preparation of methyl 1,3-*O*-isopropylidene-α-D-fructofuranoside and 2,3:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal from sucrose. The former is readily isolated as 6-*O*-tosylate, which is a potentially useful precursor for 6-*C*-substituted D-fructose derivatives.



Scheme 2.

3. Experimental

3.1. General methods

All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(A) 1:3, (B) 1:1 EtOAc–hexane, and (C) EtOAc]. Column chromatography was performed on Katayama Silica Gel 60K070. The components were detected by exposing the plates to UV light and/or spraying them with 20% H_2SO_4–EtOH (with subsequent heating). Optical rotations were measured with a JASCO P-1020 polarimeter in $CHCl_3$. The ^1H NMR spectra were measured in $CDCl_3$ with Varian Unity Inova AS600 (600 MHz) at 23 °C. Chemical shifts are reported as δ values relative to $CHCl_3$ (7.26 ppm) as an internal standard.

3.2. Acetalation and subsequent acetylation of sucrose

To a solution of sucrose (500 mg, 1.46 mmol) in dry 1,4-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 dry pyridine (7.5 mL) and acetic anhydride (2.5 mL, 26 mmol) was added at 0 °C. The mixture was stirred at rt for 12 h, diluted with a small amount of cold water, 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 column chromatography with a gradient eluent of 1:7–1:3 EtOAc–hexane into six fractions, A–F.

Fraction A [R_f 0.58 (A)] gave (1*S*)-1,2:3,4:5,6-tri-*O*-isopropylidene-1-methoxy-D-glucitol (**4a**)[14,15] (24.3 mg, 5.0% from sucrose) as a colorless syrup: ^{1}H NMR, see Table 2.

Fraction B [R_f 0.45 (A)] gave methyl 2,3:4,6-di-*O*-isopropylidene-α-D-glucoseptanoside (**12**)[16] (6.7 mg, 1.7%) as a colorless syrup (lit.[16] mp 64–65 °C): ^{1}H NMR, see Table 2.

Fraction C [R_f 0.40 (A)] gave a colorless syrup, which consisted of (1*R*)-1,2:3,4:5,6-tri-*O*-isopropylidene-1-methoxy-D-glucitol (**4b**)[15] (6.5 mg, 1.3%), 6-*O*-acetyl-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (**8**)[16,17] (2.9 mg, 0.7%), and 1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-α-D-glucoseptanose (**13a**)[16] (2.9 mg, 0.7%), the ratio being estimated by ^{1}H NMR: ^{1}H NMR, see Table 2.

Fraction D [R_f 0.35–0.32 (A)] gave a colorless syrup, which consisted of 2-*O*-acetyl-3,4:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal (**5**) (49.6 mg, 9.8%), 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**)[14,18] (21.1 mg, 4.8%), and 3-*O*-acetyl-1,2:4,6-di-*O*-isopropylidene-α-D-glucopyranose (**9**)[14] (9.2 mg, 2.1%), the ratio being estimated by ^{1}H NMR: ^{1}H NMR, see Table 2.

Fraction E [R_f 0.28–0.25 (A)] gave a colorless syrup, which consisted of 4-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal (**6**) (247 mg, 49%), methyl 2,3-di-*O*-acetyl-4,6-*O*-isopropylidene-α-D-glucopyranoside (**10a**)[19] (16.3 mg, 3.5%), and its β-D-glucopyranoside (**10b**)[19] (13.4 mg, 2.9%), the ratio being estimated by ^{1}H NMR: ^{1}H NMR, see Table 2. Rechromatography of this fraction afforded **6** as a colorless syrup: $[\alpha]_D^{21}$ +2.28 (*c* 1.62). Anal. Calcd for $C_{16}H_{28}O_8$: C, 55.16; H, 8.10. Found: C, 55.09; H, 8.16.

Fraction F [R_f 0.16 (A)] gave methyl 4,6-di-*O*-acetyl-1,3-*O*-isopropylidene-α-D-fructofuranoside (**14**)[14] (316 mg, 68%) as a colorless syrup: $[\alpha]_D^{17}$ +29.6 (*c* 1.02) [lit.[14] $[\alpha]_D^{20}$ +35.5 (*c* 1, $CHCl_3$)]; ^{1}H NMR, see Table 3.

3.3. Acetalation and subsequent acetylation of D-glucose

By use of the same procedures just described, D-glucose (500 mg, 2.78 mmol) was treated with 2,2-dimethoxypropane (2.5 mL) and *p*-toluenesulfonic acid monohydrate (40 mg) and then acetylated. The products were separated by column chromatography into six fractions, A–F.

Fraction A [R_f 0.58 (A)] gave **4a** (74.4 mg, 8.1% from D-glucose) as a colorless syrup.

Fraction B [R_f 0.45 (A)] gave **12** (5.2 mg, 0.7%) as a colorless syrup.

Fraction C [R_f 0.40 (A)] gave an inseparable mixture of **4b** (45.6 mg, 4.6%), **8** (17.1 mg, 2.0%), and **13a** (10.0 mg, 1.2%).

Fraction D [R_f 0.35–0.32 (A)] gave an inseparable mixture of **5** (66.6 mg, 6.9%), **7** (143 mg, 17%), and **9** (28.5 mg, 3.4%).

Fraction E [R_f 0.28 (A)] gave 4-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal (**6**) (398 mg, 41%) as a colorless syrup.

Fraction F [R_f 0.22 (A)] gave 1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-β-D-glucoseptanose (**13b**)[16] (30.0 mg, 3.6%) as colorless prisms: mp 98–99 °C (lit.[16] mp 99–100 °C); ^{1}H NMR, see Table 2.

3.4. Acetalation and subsequent acetylation of D-fructose

By use of the same procedures already described, D-fructose (500 mg, 2.78 mmol) was treated with 2,2-dimethoxypropane (2.5 mL) and *p*-toluenesulfonic acid monohydrate (40 mg) and then acetylated. The products were separated by column chromatography into five fractions, A–E.

Fraction A [R_f 0.53 (A)] gave an inseparable mixture (1:1) of (2*R*)- and (2*S*)-1,2:3,4:5,6-tri-*O*-isopropylidene-2-methoxy-D-*arabino*-hexitols (**15a**,**b**) (92.3 mg, 10% from D-fructose) as a colorless syrup: ^{1}H NMR, see Table 3.

Fraction B [R_f 0.42 (A)] gave 3-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**18**)[20,21] (301 mg, 36%) as colorless needles: mp 76–77 °C (lit.[21] mp 76–77 °C); ^{1}H NMR, see Table 3.

Fraction C [R_f 0.35 (A)] gave a colorless syrup, which consisted of 1-*O*-acetyl-3,4:5,6-di-*O*-isopropylidene-D-fructose (**16**) (48.0 mg, 5.7%) and 1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**19**)[20] (20.2 mg, 2.4%), the ratio being estimated by ^{1}H NMR: ^{1}H NMR, see Table 3.

Fraction D [R_f 0.26 (A)] gave a colorless syrup, which consisted of 3-*O*-acetyl-1,2:4,6-di-*O*-isopropylidene-β-D-fructofuranose (**17**) (24.5 mg, 2.9%) and methyl 1,3:4,5-di-*O*-isopropylidene-β-D-fructopyranoside (**20**) (36.4 mg, 4.8%), the ratio being estimated by ^{1}H NMR: ^{1}H NMR, see Table 3.

Fraction E [R_f 0.16 (A)] gave **14** (60.9 mg, 6.9%) as a colorless syrup.

3.5. Methyl 1,3-*O*-isopropylidene-α-D-fructofuranoside (3)[14]

To a solution of **14** (231 mg, 0.276 mmol) in dry MeOH (5.0 mL) was added, with stirring, a 28% methanolic solution of NaOMe (0.03 mL, 0.15 mmol) at 0 °C. After having been stirred at rt for 1 h, the mixture was neutralized with Amberlite IR-120(H^+). The resin was filtered off and washed with MeOH. The filtrate was evaporated in vacuo and the residue was purified by column chromatography to give **3** (167 mg, 98%) as a colorless syrup: $[\alpha]_D^{20}$ +41.9 (*c* 1.11) [lit.[14] 92% yield, $[\alpha]_D^{20}$ +42.5 (*c* 1,

MeOH)]; R_f 0.07 (B), 0.32 (C); ^{1}H NMR: δ 1.39, 1.48 (3H each, 2s, CMe_2), 2.35 (2H, br s, HO-4,6), 3.33 (3H, s, MeO-2), 3.80 (1H, dd, $J_{6,6'}$ 11.7, $J_{5,6'}$ 5.4 Hz, H′-6), 3.86 (1H, dd, $J_{5,6}$ 3.2 Hz, H-6), 3.93 (1H, d, $J_{1,1'}$ 12.2 Hz, H,H′-1), 3.99 (1H, dd, $J_{4,5}$ 2.5, $J_{3,4}$ 0.5 Hz, H-4), 4.05 (1H, d, H-3), 4.16 (1H, ddd, H-5).

3.6. 2,3:5,6-Di-*O*-isopropylidene-D-glucose dimethyl acetal (21)[15]

By use of the same procedures already described, compound **6** (98.6 mg) was treated with NaOMe to give **21** (83.3 mg, 96%) as a colorless syrup: $[\alpha]_D^{20}$ −8.17 (*c* 2.16) [lit.[15b] $[\alpha]_D^{22}$ −15 (*c* 3.1, MeOH)]; R_f 0.13 (A); ^{1}H NMR: δ 1.36, 1.42, 1.43, 1.435 (3H each, 4s, CMe_2), 2.14 (1H, br s, HO-4), 3.42, 3.43 (3H each, 2s, MeO-1), 3.61 (1H, br d, H-4), 4.02 (1H, dt, $J_{4,5}$ 8.1, $J_{5,6}$ 5.4, $J_{5,6'}$ 5.4 Hz, H-5), 4.07 (2H, d, H,H′-6), 4.125 (1H, dd, $J_{2,3}$ 8.3, $J_{1,2}$ 6.6 Hz, H-2), 4.18 (1H, dd, $J_{3,4}$ 1.2 Hz, H-3), 4.40 (1H, d, H-1).

3.7. Methyl 1,3-*O*-isopropylidene-6-*O*-tosyl-α-D-fructofuranoside (22) and its 4,6-di-*O*-tosyl analog (23)

3.7.1. From 3. To a solution of **3** (98.0 mg, 0.418 mmol) in dry pyridine (2.0 mL) was added, with stirring, tosyl chloride (95.0 mg, 0.498 mmol) at 0 °C. The mixture was stirred at rt for 12 h, diluted with a small amount of cold water, and 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 column chromatography to give **22** and **23**.

Compound **22**: colorless syrup (137 mg, 84%); $[\alpha]_D^{16}$ +30.3 (*c* 1.02); R_f 0.05 (A), 0.32 (B); ^{1}H NMR: δ 1.23, 1.40 (3H each, 2s, CMe_2), 2.44 (3H, s, CH_3C_6–S), 2.68 (1H, br s, HO-4), 3.27 (3H, s, MeO-2), 3.83 (1H, m, H-4), 3.85, 3.87 (1H each, 2d, $J_{1,1'}$ 12.2 Hz, H,H′-1), 3.98 (1H, d, $J_{3,4}$ 0.7 Hz, H-3), 4.12 (1H, dd, $J_{6,6'}$ 10.3, $J_{5,6'}$ 6.1 Hz, H′-6), 4.16 (1H, dd, $J_{5,6}$ 6.8 Hz, H-6), 4.23 (1H, ddd, $J_{4,5}$ 2.0 Hz, H-5), 7.33, 7.81 (1H each, 2d, *J* 8.3 Hz, C_6H_4-S). Anal. Calcd for $C_{17}H_{24}SO_8$: C, 52.57; H, 6.23. Found: C, 52.76; H, 6.31.

Compound **23**: colorless prisms (11.8 mg, 5.2%); mp 118–119 °C (from 2:1 AcOEt–hexane); $[\alpha]_D^{16}$ +35.4 (*c* 1.00); R_f 0.13 (A), 0.52 (B); ^{1}H NMR: δ 1.215, 1.225 (3H each, 2s, CMe_2), 2.44, 2.46 (3H each, 2s, CH_3C_6–S), 3.18 (3H, s, MeO-2), 3.70, 3.79 (1H each, 2d, $J_{1,1'}$ 12.5 Hz, H,H′-1), 3.94 (1H, d, $J_{3,4}$ 0.5 Hz, H-3), 4.11 (1H, d, $J_{5,6}$ 5.1 Hz, H_2-6), 4.16 (1H, td, $J_{4,5}$ 3.9 Hz, H-5), 4.47 (1H, dd, H-4), 7.33, 7.36, 7.77, 7.78 (1H each, 4d, *J* 8.1 Hz, C_6H_4–S). Anal. Calcd for $C_{24}H_{30}S_2O_{10}$: C, 53.13; H, 5.57. Found: C, 53.33; H, 5.64.

3.7.2. From sucrose. To a solution of sucrose (500 mg, 1.46 mmol) in dry 1,4-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. The mixture was neutralized with pyridine at rt and concentrated in vacuo. The residue was treated with tosyl chloride (278 mg, 1.46 mmol) and dry pyridine (7.5 mL) with the procedures already described. The products were separated by column chromatography with a gradient eluent of 1:3–1:1 EtOAc–hexane. After elution of the fractions [R_f 0.58–0.10 (A), 0.84–0.46 (B)], which consisted of D-glucose acetals (380 mg), the slowest-eluting fraction [R_f 0.32 (B)] gave **22** (274 mg, 48%) as a colorless syrup.

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