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Note

D-Fructose–L-sorbose interconversions. Access to 5-thio-D-fructose and interaction with the D-fructose transporter, GLUT5

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Dedicated to Professor Gerard Descotes on the occasion of his retirement

Abstract

Epimerisation and subsequent functionalization at C-5 of D-fructopyranose derivatives under Mitsunobu and Garegg's conditions provided efficient access to 5-thio-D-fructose (**2**) as well as to 5-azido-5-deoxy-1,2-*O*-isopropylidene-β-D-fructopyranose (**19**), a known precursor to 2,5-deoxy-2,5-imino-D-mannitol (**3**). The interaction of **2** with the D-fructose transporter GLUT5, was found to be weaker than that of D-fructose, a result that suggests involvement of the ring oxygen atom in the recognition of D-fructose by GLUT5. © 2001 Elsevier Science Ltd. All rights reserved.

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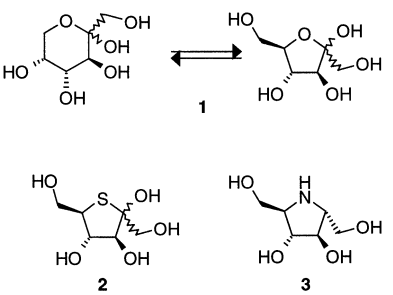
The chemistry of D-fructose **1** (Scheme 1) has not been as much developed as that of D-glucose even though it is one of the most abundant simple sugars in nature and is industrially produced.[1] The objective of the studies described here is primarily the development of inhibitors of glycosidases and of D-fructose-transporters.[2] Specifically fructofuranose mimics, 5-thio-D-fructose (**2**)[3] and 2,5-dideoxy-2,5-imino-D-mannitol (**3**)[4] (Scheme 1) were privileged targets within our project.[5] We report in this note a straightforward method of stereoselective functionalization of D-fructose with sulfur or nitrogen at C-5 and the subsequent cyclization process leading to **2** and to a precursor of **3**.



Scheme 1.

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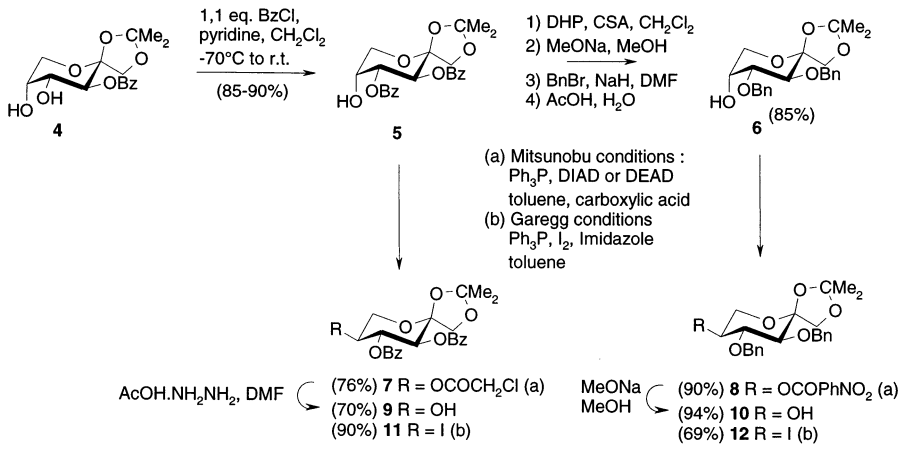


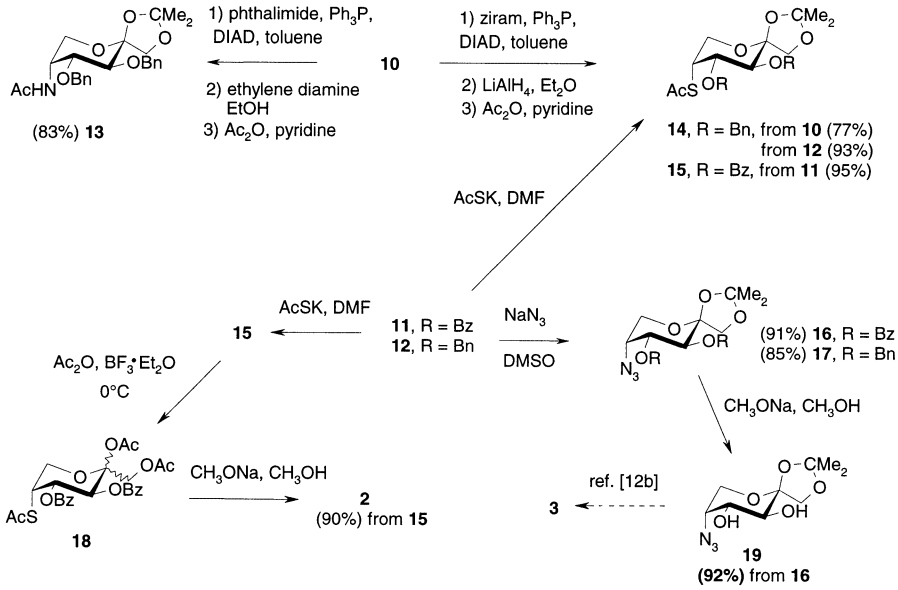
Scheme 2.

Our sequence started with established procedures[6] from 1,2;4,5-di-*O*-isopropylidene-β-D-fructopyranose involving protection of the isolated hydroxyl group by benzoylation followed by selective acidic hydrolysis to generate our starting material **4** in good yield. The selective 4-O-acylation or silylation of **4** has been previously reported.[6,7] 4-O-Benzoylation was optimized and provided **5** in 85–90% yield at low temperature (-65 °C) in a CH_2Cl_2–pyridine mixture. Changing the *O*-benzoyl protecting groups of **5** into benzyl groups could be achieved by an efficient four-step sequence (Scheme 2). A THP group was first introduced at O-5 under standard conditions in 98% yield. After methanolysis of the benzoates (94% yield), benzylation of the free hydroxyls was performed in 91% yield. Final acid hydrolysis of the THP group gave 1,2-*O*-isopropylidene-3,4-di-*O*-benzyl-β-D-fructopyranose (**6**) in nearly quantitative yield. This sequence could be carried out on a multigram scale without purification of the intermediates, thus providing **6** in nearly 85% overall yield.

Epimerisation at C-5 in both compounds **5** and **6** was faced in order to prepare L-sorbopyranose derivatives. Under standard Mitsunobu conditions[8] using chloroacetic acid and *p*-nitrobenzoic acid, compounds **5** and **6** gave esters **7** and **8** in 76 and 90% yields, respectively. Selective deprotection of the chloroacetyl and nitrobenzoyl groups using hydrazine acetate and Zemplen conditions, respectively, gave the L-sorbopyranose derivatives **9** and **10** in 70 and 94% yield respectively. Under Garegg's conditions,[9] the 5-deoxy-5-iodo-L-sorbopyranose derivatives **11** and **12** were obtained in 90 and 69% yield from **5** and **6**, respectively. To our knowledge, these are the first examples of conversion of D-fructose to L-sorbose derivatives by means of Mitsunobu and Garegg's conditions (Scheme 2). These efficient procedures were used to perform a second epimerization in order to prepare 5-amino-5-deoxy- and 5-thio-D-fructopyranose derivatives.

Mitsunobu conditions were applied to compounds **9** and **10** to introduce nitrogen via a phthalimido group and sulfur by way of a dithiocarbamate functionality[10] (Scheme 3). In all cases, complete transformations occurred but the products were contaminated with diethyl hydrazodicarboxylate ($DEADH_2$) even after chromatography. Pure compounds could be isolated from **10** after two further steps: (i) the phthalimido group was removed with ethylenediamine and the amino group thus released was acetylated to give compound **13** in 83% overall yield; (ii) the dithiocarbamate functionality was reduced with LAH into a thiol that was then acetylated to **14** in 77% overall yield.

Another method for the introduction of nitrogen and sulfur was based on nucleophilic displacements of iodine in 5-deoxy-5-iodo-L-sorbopyranose derivatives bearing either benzoyl (**11**) or benzyl (**12**) protective groups. Using potassium thioacetate in DMF, excellent yields were obtained (93% for **14** and 95% for **15**). Sodium azide in DMF proved to be



Scheme 3.

less efficient on the benzoate **11**, in which case only 50% of **16** was isolated. By changing the solvent to Me_2SO, however, a clean displacement occurred and azides **16** and **17** were obtained in very good yields (91 and 85%, respectively).

The benzylated thioacetate **14** could thus be reached either by way of the Mitsunobu reaction or by the Garegg's reaction. Both routes were competitive in terms of yields, though the Mitsunobu approach required three more steps. The benzoylated thioacetate **15** was reached more conveniently using the Garegg's reaction. No attempts were made to obtain this product through a Mitsunobu approach because of the multistep process required.

All D-fructopyranose and L-sorbopyranose derivatives **7**–**17** were shown to exist in a $^2C_5$ conformation in solution. This was confirmed by the magnitude of the $^3J_{3,4}$ coupling constant (8.5–10.7 Hz). The epimerisation process was monitored by the $^3J_{4,5}$ values which ranged for D-fructopyranose compounds between 3.4 and 4.7 Hz and for L-sorbopyranose derivatives between 9.4 and 10.0 Hz (Tables 1 and 2).

The procedures described are efficient pathways to thio- and amino- functionalization at C-5 of D-fructose. As a first development of these results, the synthesis of 5-thio-D-fructose (**2**) was performed. The thioacetate **15** smoothly underwent acetolysis into **18** in 90% yield. The anomers **18α** and **18β** could be separated by chromatography (1:4 ratio). NMR spectroscopy clearly showed that **18β** was in the usual $^2C_5$ conformation whereas **18α** was in a $^5C_2$ conformation.

A standard transesterification process in methanol then gave 5-thio-D-fructose (**2**) in nearly quantitative yield. Moreover, when a transesterification of **16** was performed under the same conditions, the well-known precursor **19** of 2,5-dideoxy-2,5-imino-D-mannitol (**3**) was prepared in very good yield.

In conclusion, we have further explored the selective functionalization of D-fructopyranose at C-5 and its epimerisation into L-sorbose compounds using Mitsunobu and Garegg's methodologies. Advantage was taken of the reactivity of the C-5 hydroxyl to provide a new efficient access to 5-thio-D-fructose (**2**) in eight steps from D-fructose and in 20–25% overall yield. Access to **19** was also efficient, in seven steps and 25–30% overall yield.

Biological studies of **2** as a GLUT5 inhibitor were undertaken with CHO cell line in which GLUT 5 transporter is expressed at high levels.[2] The substrate for the assays is a tracer concentration (1 mM) of [^{14}C-U]-D-fructose. First results showed a weak inhibition constant of 96 mM. This indicates that the affinity is at least six-times lower than for

Table 1
^{1}H NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) for 1,2-*O*-isopropylidene D-fructopyranose- and L-sorbopyranose derivatives

	H-1a	H-1b	H-3	H-4	H-5	H-6a	H-6b	specific protons	$C(CH_3)_2$
6	3.93 (d) $J_{1a,1b}$ 12.6	3.97 (d)	3.77(d) $J_{3,4}$ 9.4	3.95 (dd) 3.4	4.04 (ddd) $J_{5,6a}$ 1.7	3.80 (dd) $J_{6a,6b}$ 13.0	3.93 (dd) $J_{5,6b}$ 1.5	2.4 (OH, s)	1.43 1.49
7	3.96–4.12 n.d. [a]	3.96–4.12 n.d. [a]	5.51 (d) $J_{3,4}$ 9.8	5.93 (dd) $J_{4,5}$ 9.8	5.33 (ddd) $J_{5,6a}$ 6.4, $J_{5,6b}$ 10.4	3.96–4.12 n.d. [a]	3.96–4.12 n.d. [a]		1.42 1.54
	3.89 (d) $J_{1a,1b}$ 8.7	3.97 (d)	5.54 (d) $J_{3,4}$ 9.4	4.14 (dd) $J_{4,5}$ 9.4	5.24 (ddd) $J_{5,6a}$ 10.6	3.77 (dd) $J_{6a,6b}$ 10.9	3.91 (dd) $J_{5,6b}$ 6.2		1.48 1.51
9	3.83–4.14 n.d. [a]	3.83–4.14 n.d. [a]	5.47 (d) $J_{3,4}$ 9.8	5.56 (dd) $J_{4,5}$ 10.0	3.83–4.14 n.d. [a]	3.83–4.14 n.d. [a]	3.83–4.14 n.d. [a]	3.7 (OH, d) $J_{OH,5}$ 4.9	1.43 1.54
10	3.87 (d) $J_{1a,1b}$ 8.5	3.91 (d)	3.39 (d) $J_{3,4}$ 9.00	3.69–3.77 n.d. [a]	3.69–3.77 n.d. [a]	3.69–3.77 n.d. [a]	3.69–3.77 n.d. [a]	2.05 (OH, s)	1.44 1.50
11	3.99 (d) $J_{1a,1b}$ 9.4		5.40 (d) $J_{3,4}$ 9.7	5.96 (dd) $J_{4,5}$ 10.05	4.16–4.34 n.d. [a]	3.94–4.1 n.d. [a]	4.16–4.34 n.d. [a]		1.41 1.54
12	3.81 (d) $J_{1a,1b}$ 8.5	3.89 (d) $J_{3,4}$ 8.5	3.38 (d) n.d. [a]	3.79–4.11 n.d. [a]	3.79–4.11 n.d. [a]	3.79–4.11 n.d. [a]	3.79–4.11 n.d. [a]		1.45 1.50
13	3.87 (d) $J_{1a,1b}$ 9.5	3.96 (d)	3.53 (d) $J_{3,4}$ 9.8	4.01 (dd) $J_{4,5}$ 4.7	4.6 (m)	3.70 (dd) $J_{6a,6b}$ 12.1 $J_{5,6a}$ 1.8	3.98 (dd) $J_{5,6b}$ 1.9	2.00 ($COCH_3$) 6.53 ($NHCOCH_3$, d) $J_{NH,5}$ 8.31	1.47 1.42
14	3.87 (d) $J_{1a,1b}$ 8.5	3.92 (d)	3.38 (d) $J_{3,4}$ 9.8	4.18 (dd) $J_{4,5}$ 4.7	4.35 (m)	3.69 (dd) $J_{6a,6b}$ 12.4 $J_{5,6a}$ 1.9	4.24 (dd) $J_{5,6b}$ 2.2	2.39 ($COCH_3$)	1.42 1.46
15	4.07 (d) $J_{1a,1b}$ 9.4	4.00 (d)	5.60 (d) $J_{3,4}$ 10.7	5.88 (dd) $J_{4,5}$ 4.7	4.49 (m)	3.85 (dd) $J_{6a,6b}$ 12.2 $J_{5,6a}$ 1.3	4.53 (dd) $J_{5,6b}$ 2.2	2.24 ($COCH_3$)	1.43 1.53
16	4.02 (d) 9.4	4.10 (d)	5.87 (d) $J_{3,4}$ 10.4	5.78 (dd) $J_{4,5}$ 3.4	4.31 (ddd) $J_{5,6a}$ 1.7	3.88 (dd) $J_{6a,6b}$ 12.6	4.24 (dd) $J_{5,6b}$ 1.7		1.43 1.53
17	3.92 (d) 8.5	3.94 (d)	3.77 (d) 9.6	4.05 (dd) 3.7	3.91 (m)	3.65 (dd) $J_{6a,6b}$ 12.8 $J_{5,6a}$ 1.1	3.90 (dd) $J_{5,6b}$ 1.7		1.42 1.46

[a] n.d., not determined.

Table 2
^{13}C NMR chemical shifts (δ in ppm) for 1,2-*O*-isopropylidene D-fructopyranose- and L-sorbopyranose derivatives

	C-1	C-2	C-3	C-4	C-5	C-6	$C(CH_3)_2$	Specific carbons
6	71.7	105.6	74.5	80.1	67.1	62.9	26.1, 26.9, 111.9	CH_2Ph 72.1, 75.3
7	71.6	104.0	69.4	71.6	71.1	60.0	26.2, 26.6, 113.0	$COCH_2Cl$ 40.5, 165.8
8	71.5	105.1	78.3	81.3	72.8	59.9	26.2, 27.2, 112.5	CH_2Ph 75.5, 75.6 OCOPh 163.8 C–NO_2 150.6
9	71.8	104.0	69.0	76.9	69.9	63.5	26.3, 26.7, 112.7	
10	71.5	105.3	78.4	84.2	70.2	62.9	26.3, 27.2, 112.2	CH_2Ph 2 × 75.4
11	71.8	104.6	71.0	74.3	22.0	65.9	26.1, 26.7, 112.8	
12	71.6	105.8	80.4	84.0	26.8	65.9	26.2, 27.2, 112.5	CH_2Ph 75.4, 75.7
13	71.9	105.3	75.0	78.1	47.5	62.6	26.3, 27.1, 112.4	CH_2Ph 71.4, 75.4 $COCH_3$ 23.5, 170.5
14	71.9	105.6	76.4	78.1	45.5	63.7	26.1, 27.1, 112.3	CH_2Ph 71.6, 75.3 $COCH_3$ 31.0, 195.1
15	71.9	104.7	68.4	69.9	45.5	63.8	26.1, 26.5, 112.5	$COCH_3$ 30.5, 193.5
16	71.8	104.7	67.2	71.7	60.2	62.1	26.2, 26.5, 112.5	
17	71.8	105.7	75.0	80.0	60.1	61.8	26.1, 27.0, 112.2	

D-fructose.[2] Therefore, a single change of oxygen into sulfur atom in the ring markedly changes the interaction with the GLUT5 binding site. This result demonstrates that the ring oxygen of D-fructofuranose is involved in GLUT5 binding.

1. Experimental

General methods.—Melting points were determined on a Büchi 510 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with Me_4Si as internal standard; for other solvents, the residual peak was used as internal standard. Whenever appropriate, signal assignments were deduced by DEPT, COSY and HETCOR NMR experiments. Specific rotations were measured at 20 °C using a Perkin–Elmer 141 polarimeter. Low resolution mass spectra (MS) were recorded by the ICOA Analytical Service on a Perkin–Elmer SCIEX API 300 (ion spray). Elemental analysis was performed by the microanalytical service at the University of Bath and by the analytical service of the CNRS, Vernaison. Analytical TLC was carried out on precoated Silica Gel 60F-254 plates (E. Merck) and spots were detected by UV light (254 nm) and by spraying with a 5% H_2SO_4 ethanolic solution followed by heating. Column chromatography was performed on Silica Gel SI 60 (43–60 μm) (E. Merck).

3,4-Di-O-*benzyl-1,2*-O-*isopropylidene-β*-D-*fructopyranose* (**6**).—To a solution of 3,4-di-*O*-benzoyl-1,2-*O*-isopropylidene-β-D-fructopyranose (**5**)[6] (5.7 g, 13.3 mmol) and dihydropyran (8 mL, 87.7 mmol) in dry CH_2Cl_2 was added camphorsulfonic acid (0.05 g, 0.21 mmol). The mixture was left under Ar at rt for 2 h. After alcalinisation with triethylamine, the solvent was removed by evaporation. The crude product was dissolved in dry MeOH (30 mL) and then Na (0.03 g, 1.3 mmol) was added to the solution, which was stirred overnight. The solution was made neutral with DOWEX 50X, and the solvent removed by evaporation. The residue was dissolved in DMF (30 mL) and after cooling in an ice-salt bath, NaH (60%, 2.3 g, 57.5 mmol) was added. After 20 min stirring, BnBr (3.5 mL, 29.5 mmol) was added dropwise. After overnight stirring, careful methanolysis (10 mL) was then effected. The mixture was diluted in water (100 mL) and extracted with EtOAc (3 × 150 mL). The combined organic fractions were washed with water (3 × 50 mL), satd NaCl (50 mL), then dried over $MgSO_4$ and evaporated to dryness. The crude mixture was treated, in the last deprotection step, with AcOH (30 mL)–water (7.5 mL) for 1 day. After extraction with EtOAc–water, alcalinisation with aq K_2CO_3, drying of the organic solution over $MgSO_4$ and evaporation of the solvent, **6** (4.5 g, 84%) was purified by flash chromatography using 7:3 petroleum ether–EtOAc: $[\alpha]_D^{20}$ −90° (*c* 1.1, $CHCl_3$); IR (NaCl) *v* 3460 (br, OH); ISMS$^{(+)}$: *m/z* 418 $[M+NH_4]^+$, 423 $[M+Na]^+$. Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.92; H, 7.00.

3,4-Di-O-*benzoyl-5*-O-*chloroacetyl-1,2*-O-*isopropylidene-β*-L-*sorbopyranose* (**7**).—To a cooled (ice-salt bath) solution containing **5** (1.9 g, 4.44 mmol), triphenylphosphine (3 g, 11.4 mmol) and chloroacetic acid (1.05 g, 11.1 mmol) in dry toluene (20 mL), DEAD (2 mL, 12.7 mmol) was slowly added. The solution was stirred at 60 °C overnight. After evaporation of the solvent, colorless crystals of **7**, (1.7 g, 76%) were obtained by silica-gel column chromatography using 8.5:1.5 petroleum ether–EtOAc: mp: 88–90 °C; $[\alpha]_D^{20}$ −139° (*c* 1.04, $CHCl_3$); IR (NaCl) *v* 1770 and 1731 cm^{-1} (esters); ISMS$^{(+)}$: *m/z* 522 $[M+NH_4]^+$, 524 $[M+NH_4]^+$, 527 $[M+Na]^+$, 529 $[M+Na]^+$. Anal. Calcd for $C_{25}H_{25}ClO_9$: C, 59.47; H, 4.99. Found: C, 59.12; H, 5.09.

3,4-Di-O-*benzyl-1,2*-O-*isopropylidene-5*-O-p-*nitrobenzoyl-β*-L-*sorbopyranose* (**8**).—Same conditions as those applied to **5** for **6** (1.245 g, 3.11 mmol), with some modifications: the reaction was carried out at rt with *p*-nitrobenzoic acid and the chromatography was performed with 9:1 petroleum ether–EtOAc. **8** (1.17 g, 94%) was obtained as pale yellow crystals: mp 94–95 °C; $[\alpha]_D^{20}$ +53° (*c* 1.09, $CHCl_3$); IR (NaCl) *v* 1731 cm^{-1} (esters); ISMS$^{(+)}$: *m/z* 567 $[M+NH_4]^+$, 572 $[M+Na]^+$. Anal. Calcd for $C_{30}H_{31}NO_9$: C, 65.56; H, 5.69. Found: C, 65.84; H, 5.70.

3,4-Di-O-*benzoyl-1,2*-O-*isopropylidene-β*-L-*sorbopyranose* (**9**).—To a solution of **7** (0.927

g, 1.84 mmol) in MeOH (30 mL) hydrazine acetate (0.18 g, 1.95 mmol) was added. The mixture was stirred at rt until completion. After evaporation of the solvent, **9** (0.51 g, 65%) was purified by chromatography using petroleum ether–EtOAc (4:1): mp 150–151 °C; $[\alpha]_D^{20}$ −161° (*c* 1.17, $CHCl_3$); IR (NaCl) *v* 3468 (br, OH), 1729 cm^{-1} (esters); $ISMS^{(+)}$: *m/z* 446 $[M+NH_4]^+$, 451 $[M+Na]^+$. Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.42; H, 5.61.

3,4-Di-O-*benzyl-1,2*-O-*isopropylidene-β*-L-*sorbopyranose* (**10**).—The ester **8** (1.533 g, 2.8 mmol) was deacylated using standard Zemplen conditions. After completion of the reaction, the solvent was removed. The crude mixture was purified by flash chromatography using 4:1 petroleum ether–EtOAc yielding **10** (1.05 g, 94%): mp 79–80 °C; $[\alpha]_D^{20}$ −32° (*c* 1.08, $CHCl_3$); IR (NaCl) *v* 3449 cm^{-1} (br, OH); $ISMS^{(+)}$: *m/z* 418 $[M+NH_4]^+$, 423 $[M+Na]^+$. Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.93; H, 7.11.

3,4-Di-O-*benzoyl-5-deoxy-5-iodo-1,2-O-isopropylidene-β-L-sorbopyranose* (**11**).—Compound **5** (1 g, 2.33 mmol), triphenylphosphine (1.9 g, 7.25 mmol), imidazole (0.5 g, 7.35 mmol) and iodine (1.25 g, 4.84 mmol) were dissolved in dry toluene (35 mL). The mixture was maintained at 60 °C for 5 days, then evaporated and purified by flash column chromatography, 9:1 petroleum ether–EtOAc yielding **11** (1.15 g, 91%): mp 152–153 °C; $[\alpha]_D^{20}$ −102° (*c* 1.02, $CHCl_3$); IR (NaCl) *v* 1731 cm^{-1} (esters); $ISMS^{(+)}$: *m/z* 556 $[M+NH_4]^+$, 561 $[M+Na]^+$. Anal. Calcd for $C_{23}H_{23}IO_7$: C, 51.32; H, 4.31. Found: C, 51.71; H, 4.35.

3,4-Di-O-*benzyl-5*-O-*deoxy-5-iodo-1,2*-O-*isopropylidene - β - L - sorbopyranose* (**12**).—Compound **6** (0.12 g, 0.3 mmol) gave **12** (0.1 g, 66%) under the same conditions as those applied for **11**: mp 85–87 °C; $[\alpha]_D^{20}$ +17° (*c* 1.05, $CHCl_3$); $ISMS^{(+)}$: *m/z* 528 $[M+NH_4]^+$, 533 $[M+Na]^+$. Anal. Calcd for $C_{23}H_{27}IO_5$: C, 54.13; H, 5.33. Found: C, 54.37; H, 5.34.

5-Acetamido-3,4-di-O-*benzyl-5-deoxy-1,2*-O-*isopropylidene-β*-D-*fructopyranose* (**13**).—Same protocol as for **7**, using precursor **10** (1 g, 2.5 mmol), but the reaction was carried out at rt overnight and purification was effected using 4:1 petroleum ether–EtOAc. The phthalimido compound contaminated with $DIADH_2$ was deprotected in EtOH (50 mL) with ethylenediamine (0.95 mL, 14.2 mmol) and overnight reflux, then purified after evaporation by chromatography using a mixture 45:4:1 EtOAc–MeOH–water. The crude amine was directly acetylated using pyridine (3 mL) and Ac_2O (3 mL), yielding **13** (0.915 g, 83%) over three steps without further purification: $[\alpha]_D^{20}$ −81° (*c* 1, $CHCl_3$); IR (NaCl) *v* 3293 (br, NH), 1651 cm^{-1} (amide); $ISMS^{(+)}$: *m/z* 443 $[M+NH_4]^+$. Anal. Calcd for $C_{25}H_{31}O_6N$: C, 68.01; H, 7.08 Found: C, 67.78; H, 7.13.

5-S-*Acetyl-3,4-di*-O-*benzyl-1,2*-O-*isopropylidene - 5 - thio - β* - D - *fructopyranose* (**14**).—Method A: The same protocol as for **7**, using precursor **10** (0.4 g, 1 mmol). The dithiocarbamate contaminated with $DIADH_2$ was diluted with Et_2O (20 mL) and LAH (0.098 g, 2.6 mmol) was added portionwise. The solution was stirred at rt for 48 h. The workup was effected by the addition of ice and acidification to pH 1 with HCl 2 M, then extracted twice with EtOAc. The organic layers were collected, washed with water until neutral and dried over $MgSO_4$. After evaporation, the crude thiol was diluted with pyridine (5 mL) and Ac_2O (2 mL). After 24 h stirring at rt, the solvents were removed by coevaporation with toluene, and **14** crystallized in EtOH–water mixture (0.356 g, 77%): mp 79–81 °C; $[\alpha]_D^{20}$ −89° (*c* 1.09, $CHCl_3$); IR (NaCl) *v* 1691 cm^{-1} (thioester); $ISMS^{(+)}$: *m/z* 476 $[M+NH_4]^+$, 481 $[M+Na]^+$. Anal. Calcd for $C_{25}H_{30}O_6S$: C, 65.48; H, 6.59. Found: C, 65.67; H, 6.65.

Method B: Compound **12** (0.07 g, 0.14 mmol) diluted in DMF (2 mL) was mixed with AcSK (0.05 g, 0.51 mmol). The solution was heated at 100 °C for 2 h. After dilution in AcOEt, the organic phase was washed with water (four times) and brine. The organic layer was further dried over $MgSO_4$ and decolorized with activated carbon. After filtration on a short Celite® pad, evaporation of the solvent yielded pure **14** (0.061 g, 93%).

5-S-*Acetyl-3,4-di*-O-*benzoyl-1,2*-O-*isopropylidene-5-thio-β*-D-*fructopyranose* (**15**).—The iodinated-derivative **11** (0.54 g, 1 mmol) was

diluted with DMF (4 mL) under Ar. Potassium thioacetate (0.3 g, 3 mmol) was added to the solution before heating to 100 °C for 90 min. After completion, the mixture was poured in AcOEt then washed successively with water (four times) and brine. After being dried over $MgSO_4$, decolorized with activated carbon and filtrated over Celite® pad, the mixture was evaporated to give **15** (0.435 g) of good purity. Recrystallization in petroleum–ether–Et_2O gave pure **15** (0.35 g, 72%): mp 136–138 °C; $[\alpha]_D^{20}$ −141° (*c* 1.1, $CHCl_3$); IR (NaCl) *v* 1695 (thioester), 1738 cm^{-1} (esters); ISMS$^{(+)}$: *m/z* 504.5 $[M+NH_4]^+$. Anal. Calcd for $C_{25}H_{26}O_8S$: C, 61.72; H, 5.39. Found: C, 61.45; H, 5.27.

5-Azido-3,4-di-O-*benzoyl-5-deoxy-1,2*-O-*isopropylidene-β*-D-*fructopyranose* (**16**).—The iodo derivative **11** (0.28 g, 0.52 mmol) was dissolved in Me_2SO (2 mL) and sodium azide (0.345 g, 5.3 mmol) was added. The solution was heated to 100 °C for 3 h, then poured into AcOEt. The organic solution was washed with water (three times), brine and dried over $MgSO_4$. After a short filtration over a silica gel pad and evaporation to dryness, **16** (0.215 g, 91%) was isolated: mp 84–86 °C; $[\alpha]_D^{20}$ −115° (*c* 1.15, $CHCl_3$); IR (NaCl) *v* 2101 cm^{-1} (azide), 1729 cm^{-1} (ester); ISMS$^{(+)}$: *m/z* 471 $[M+NH_4]^+$. Anal. Calcd for $C_{23}H_{23}N_3O_7$: C, 60.92; H, 5.11. Found: C, 61.24; H, 5.23.

5-Azido-3,4-di-O-*benzyl-5-deoxy-1,2*-O-*isopropylidene-β*-D-*fructopyranose* (**17**).—Same conditions as those applied to **16** for **12** (0.134 g, 0.26 mmol) for 4 days at 90 °C. After usual workup, **17** (0.094 g, 85%) was obtained: $[\alpha]_D^{20}$ −87° (*c* 1, $CHCl_3$); IR (NaCl) *v* 2107 (azide); ISMS$^{(+)}$: *m/z* 443 $[M+NH_4]^+$, 448 $[M+Na]^+$. Anal. Calcd for $C_{23}H_{27}N_3O_5$: C, 64.93; H, 6.40. Found: C, 65.03; H, 6.45.

5-S-*Acetyl-3,4-di*-O-*benzoyl-1,2-di*-O-*acetyl-5-thio*-D-*fructopyranose* (**18α**, **18β**).—Under Ar **15** (0.48 g, 1 mmol) was dissolved in Ac_2O (2.5 mL) and cooled (ice-salt bath) to −10 °C. $BF_3{\cdot}Et_2O$ (0.1 mL) was added slowly. After 90 min, the solution was diluted with EtOAc, washed twice with ice cold water and satd $NaHCO_3$ then brine. The organic phase was dried over $MgSO_4$, evaporated under reduced pressure, and purified on silica gel (4:1 petroleum ether–EtOAc,) yielding **18** (0.485 g, 92%). The crude compounds **18α**, **18β** (0.260 g) were separated on silica gel with CH_2Cl_2 as eluent yielding **18α** (0.058 g) as a syrup and **18β** (0.2 g) which spontaneously crystallized: **18α**: $[\alpha]_D^{20}$ +21° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 8.07–8.18 (m, 4 H, H_{arom}), 7.60–7.63 (m, 4 H, H_{arom}), 7.47–7.54 (m, 4 H, H_{arom}), 5.84 (d, 1 H, H-3), 5.39 (dd, 1 H, $J_{3,4}$ 3.2 Hz, H-4), 4.85 (d, 1 H, H-1b), 4.42 (d, 1 H, $J_{1a,1b}$ 12.1 Hz, H-1a), 4.39 (ddd, 1 H, $J_{4,5}$ 3.2 Hz, H-5), 4.20 (dd, 1 H, $J_{5,6b}$ 11.9 Hz, H-6b), 3.97 (ddd, 1 H, $^4J_{6a,4}$ 1.1, $J_{6a,5}$ 5.3, $J_{6a,6b}$ 11.3 Hz, H-6a), 2.32 (s, 3 H, $SCOCH_3$), 1.96 (s, 3 H, CH_3), 1.83 (s, 3 H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.1 (SCO), 170.0, 168.4, 164.6, 164.2, 134.0, 133.9, 130.2, 129.9, 129.3, 128.9, 128.8, 128.7, 100.7 (C-2), 69.0 (C-4), 65.2 (C-3), 62.1 (C-1), 60.5 (C-6), 38.2 (C-5), 30.7 ($SCOCH_3$), 21.8 (CH_3), 20.7 (CH_3); ISMS$^{(+)}$: *m/z* 548 $[M+NH_4]^+$, 553 $[M+Na]^+$. Anal. Calcd for $C_{26}H_{28}O_8S$: C, 58.86; H, 4.94. Found: C, 59.03; H, 5.12. **18β**: mp 145–148 °C, $[\alpha]_D^{20}$ −108° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.88–7.98 (m, 4 H, H_{arom}), 7.46–7.55 (m, 4 H, H_{arom}), 7.32–7.42 (m, 4 H, H_{arom}), 5.85 (dd, 1 H, $J_{4,5}$ 3.6 Hz, H-4), 5.79 (d, 1 H, $J_{3,4}$ 10.3 Hz, H-3), 4.80 (d, 1 H, H-1b), 4.57 (d, 1 H, $J_{1a,1b}$ 11.9 Hz, H-1a), 4.53 (m, 1 H, H-5), 4.35 (dd, 1 H, $J_{5,6b}$ 2.3 Hz, H-6b), 4.02 (dd, 1 H, $J_{6a,5}$ 1.8, $J_{6a,6b}$ 12.8 Hz, H-6a), 2.29 (s, 3 H, $SCOCH_3$), 2.25 (s, 3 H, CH_3), 1.99 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5 (SCO), 169.9, 168.1, 165.5, 165.3, 132.6, 132.4, 129.8, 129.7, 129.1, 129.0, 128.6, 128.5, 102.6 (C-2), 69.1 (C-4), 68.6 (C-3), 65.1 (C-6), 63.3 (C-1), 45.0 (C-5), 31.7 ($SCOCH_3$), 21.7 (CH_3), 20.6 (CH_3); ISMS$^{(+)}$: *m/z* 548 $[M+NH_4]^+$, 553 $[M+Na]^+$. Anal. Calcd for $C_{26}H_{28}O_8S$: C, 58.86; H, 4.94. Found: C, 59.15; H, 4.90.

5-Thio-D-*fructofuranose* (**2**).—Compound **18** (0.3 g, 0.567 mmol) was diluted in MeOH and treated with sodium methoxide (0.6 mmol) at rt for 3 h. **2** (0.108 g, 97%) was isolated after purification on silica gel (20:4:1 EtOAc–MeOH–water): $[\alpha]_D^{20}$ −7° (*c* 1.1, MeOH), lit.[3] −4° (*c* 0.72, MeOH). Anal. Calcd for $C_6H_{12}O_5S$: C, 36.73; H, 6.16. Found: C, 37.01; H, 6.05.

5-Azido-5-deoxy-1,2-O-*isopropylidene-β*-D-*fructopyranose* (**19**).—Compound **16** (0.1 g,

0.22 mmol) was deacylated in MeOH (3 mL) under Ar, using Zemplen conditions at rt overnight. After completion of the reaction, SiO_2 was added to the solution and MeOH removed under reduced pressure. Compound **19** (0.05 g, 92%) was purified by column chromatography (3:2 petroleum ether–EtOAc): mp 113–114 °C, lit.[11] 114 °C.

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