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A facile synthesis of 5-thio-L-fucose and 5-thio-D-arabinose from D-arabinose

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Abstract

5-Thio-L-fucopyranose tetraacetate was synthesized in 11 steps from 5-*O*-trityl-D-arabinofuranose or D-arabinose diethyl dithioacetal by one-carbon elongation at C-5. Highly diastereoselective addition of MeLi in ether to a 1,2-*O*-isopropylidene-β-D-*arabino*-pentodialdo-1,4-furanose derivative was achieved to give the corresponding 6-deoxy-β-D-altrofuranose isomer in good yield. A sulfur atom was introduced at C-5 of 6-deoxy-D-altrofuranose derivatives via substitution of a 5-tosylate with KSAc in HMPA with inversion of configuration, giving 5-thio-L-fucopyranose. A 3-*O*-substituted-L-fucose derivative was also prepared from 6-deoxy-β-D-altrofuranose derivatives. 5-Thio-D-arabinopyranose tetraacetate, the 5-demethyl analog of 5-thio-L-fucose, was also synthesized from 5-*O*-trityl-D-arabinofuranose in 5 steps. 5-Thio-D-arabinose showed weak inhibitory activity against α-L-fucosidase from bovine kidney ($K_i = 0.77$ mM).

Keywords: Synthesis; 5-Thio-L-fucose; 5-Thio-D-arabinose

1. Introduction

5-Thio-L-fucose (**26**) [1–3] is a ring oxygen-substituted analog of normal sugars and has a specific and potent inhibitory activity against bovine α-L-fucosidases. We are interested in the synthesis and biological activities of oligosaccharides having a 5-thio-L-fucosyl residue instead of an L-fucosyl residue [4–7]. We required a large amount of **26** for syntheses of such compounds, but our first [1] and more recent [2] syntheses require 16 and 20 steps, respectively, from D-glucose and they are not convenient for large-scale preparation. Now we report here a facile synthesis of **26** from D-arabinose

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via one-carbon elongation to a D-*arabino*-pentodialdo-1,4-furanose derivative (**8**). In a similar route, we also report a synthesis of a 3-*O*-substituted-L-fucose derivative (**32**) from the inexpensive D-arabinose. Compound **32** is an alternative [8] synthetic intermediate of oligosaccharides containing the → 3)-L-Fuc-(1 → linkage, such as lipooligosaccharides from *Mycobacterium kansasii* [9].

We also synthesized 5-thio-D-arabinose (**37**), the 5-demethyl analog of **26**, in order to elucidate the contribution of the 6-methyl group to the biological activity of **26**. The first synthesis of **37** was reported by Hughes et al. [10] in 1985. Their synthesis started from 1,2-*O*-isopropylidene-5-*O*-tosyl-β-D-arabinofuranose [11] derived from D-arabinose via a trichloroethyl furanoside. Our synthesis presented here used 5-*O*-trityl-D-arabinofuranose as a starting compound.

2. Results and discussion

*Synthesis of 5-thio-*L*-fucopyranose and 3-*O*-allyl-*L*-fucopyranose triacetate.*—Selective tritylation of D-arabinose with chlorotriphenylmethane in pyridine gave 5-*O*-trityl-D-arabinofuranose (**1**, 64%) [12]. The 5-trityl ether **1** was treated with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid in acetone to give a mixture of the 1,2-*O*-isopropylidene derivative **2** as a major product and its 3-*O*-(2-methoxy-2-propyl) derivative. The latter was converted into **2** by addition of methanol, raising the yield of **2** to 72%. Allylation of **2** with sodium hydride and allyl bromide in *N,N*-dimethylformamide (DMF) afforded the 3-allyl ether **3** (77%). Detritylation was carried out by two methods. The first method, acid hydrolysis of **3** with *p*-toluenesulfonic acid monohydrate in chloroform in the presence of 2,2-dimethoxypropane, gave 3-*O*-allyl-1,2-*O*-isopropylidene-β-D-arabinofuranose (**4**) and its 5-*O*-(2-methoxy-2-propyl) derivative. After conversion of the latter byproduct into **4** in glacial acetic acid, the yield was 88%. The other method, treatment of **3** with formic acid in ether [13] yielded **4** exclusively in 64% yield. This procedure was very simple, but not suited for more than a 10-g scale of preparation, when the yield decreased to < 40%. We therefore examined an alternative route, which is similar to a synthesis of the 3-benzyl analog of **4** reported by Guilford et al. [14]. D-Arabinose diethyl dithioacetal (**5**) was benzoylated chemoselectively to give its 5-benzoate **6** (81%), which was converted in 73% yield into 5-*O*-benzoyl-1,2-*O*-isopropylidene-β-D-arabinofuranose (**7**) by treatment with mercuric chloride in dry acetone. Allylation of **7** with sodium hydride and allyl bromide in DMF and subsequent debenzoylation by addition of methanolic sodium methoxide gave **4** (73%). Large amounts of **4** could readily be obtained by this route, because compounds **5**, **6**, and **7** are all crystalline and yields were high. A dialdose derivative **8** was obtained by Swern oxidation [15] of **4** (93%).

Nucleophilic addition reactions to **8** were examined with three methyl metal reagents, namely MeMgI, MeLi, and Me_3Al and the results are shown in Table 1. Ratios between the D-*altro* (**9**) and L-*galacto* isomers (**10**) were determined by the integrated intensity of the 6-methyl signal in the ^1H NMR. Higher stereoselectivities were observed at lower temperature, except for the reaction with MeMgI in ether at −78 °C (entry 2), and the highest stereoselectivity was attained with MeLi in Et_2O at −78 °C (entry 6) and

Table 1
Nucleophilic addition reaction of **8** with some methyl carbanions

Entry	Reagent	Solvent	Conditions	Yield [a]	**9**:**10**
1	MeMgI	ether	0 °C, 30 min	82%	3:2
2	MeMgI	ether	−78 °C, 60 min	89%	3:2
3	MeMgI	THF	0 °C, 10 min	54%	4:1
4	MeMgI	THF	−20 °C, 120 min	70%	8:1
5	MeLi	ether	0 °C, 180 min	70%	6:1
6	MeLi	ether	−78 °C, 30 min	77%	> 10:1
7	MeLi	CH_2Cl_2–ether	0 °C, 180 min	70%	2:1
8	MeLi	CH_2Cl_2–ether	−78 °C, 90 min	93%	4:1
9	Me_3Al	CH_2Cl_2–hexane	−70 °C → −10 °C, 240 min	63%	> 10:1

[a] Isolated yield.

Me_3Al in CH_2Cl_2–hexane at −70 °C → −10 °C (entry 9). In all cases, the D-*altro* isomer (**9**) predominated over the L-*galacto* isomer (**10**). This stereoselectivity may be explained as follows. In the cases of MeMgI and MeLi, 6-membered ring chelation [16] (see Fig. 1) between carbonyl oxygen and O-3 is favored over 5-membered ring chelation [17] between carbonyl oxygen and ring oxygen, because the latter possibility raises steric hindrance because of the isopropylidene group attached to the same face of the furanose ring. In the case of Me_3Al, the Felkin–Ahn model provides a reasonable explanation for the stereoselectivity, as it does not involve chelation between two oxygen atoms.

The 5-epimeric pair **9** and **10** could be separated as their 5-acetates by column chromatography on silica gel, but the product obtained under the conditions of entry 6 could be used without separation for further conversions. The configuration of **9** and **10** were determined by chemical conversions into the corresponding 6-deoxyaldopyranose peracetates by removal of allyl and isopropylidene groups followed by acetylation. The peracetate derived from **10** was identified with the known L-fucopyranose tetraacetate by its ^1H NMR signals. Therefore, we concluded that **10** has the L-*galacto* configuration and **9** should have the D-*altro* configuration.

Three 5-sulfonates namely, *p*-toluenesulfonate, methanesulfonate, and trifluoromethanesulfonate, were prepared in order to examine the introduction of sulfur atom as well as inversion of configuration at C-5 by nucleophilic substitution. The D-*altro* isomer **9** was treated with *p*-toluenesulfonyl chloride in pyridine in the presence of 4-dimethylaminopyridine (DMAP) to give the 5-tosylate **11** (86%). Treatment of **9** with

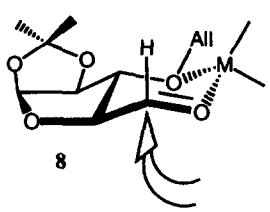

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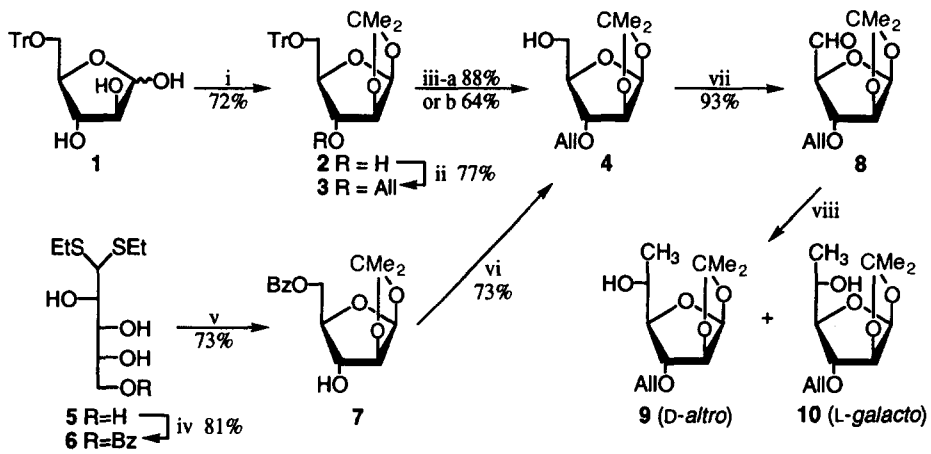
Fig. 1. Possible chelation of MeMgI and MeLi to the dialdose derivative **8**.



Scheme 1. (i) $Me_2C(OMe)_2$, $TsOH \cdot H_2O$. (ii) NaH, AllBr. (iii-a) $Me_2C(OMe)_2$, $CHCl_3$, $TsOH \cdot H_2O$, then AcOH. (iii-b) HCO_2H, Et_2O. (iv) BzCl, pyridine, −15 °C. (v) $HgCl_2$, $CuSO_4$, acetone. (vi) NaH, AllBr, 0 °C, then MeOH. (vii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N. (viii) See Table 1.

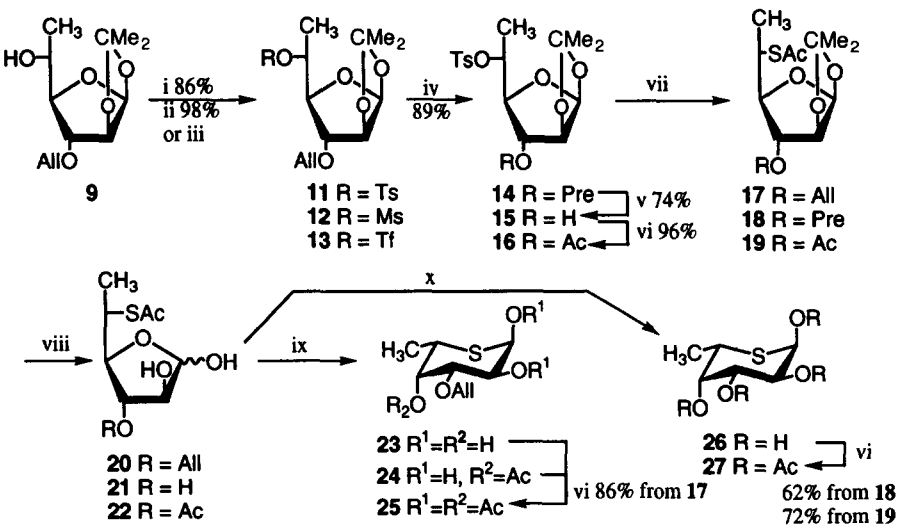
methanesulfonyl chloride in pyridine gave the 5-mesylate **12** (98%). The 5-triflate **13**, obtained by treatment of **9** with trifluoromethanesulfonic anhydride and pyridine in CH_2Cl_2 at −20 °C, was unstable and was used without purification.

The introduction of a sulfur atom by substitution reactions of the three 5-sulfonates, using potassium thioacetate is summarized in Table 2. The 5-tosylate **11** gave the best yield of the acetylated 5-thio derivative **17** (74%). Removal of the 3-*O*-allyl group of **23** with either palladium–charcoal or Wilkinson's catalyst $[Rh(PPh_3)_3Cl]$ [18] was unsuccessful because of the presence of the divalent sulfur atom. Alternative modes for protection of the 3-hydroxyl, with prop-1-enyl (**14**) and acetyl groups (**16**), were examined. The former was obtained by treatment of **11** with palladium–charcoal in methanol (89%), and the latter by treatment of **11** with Wilkinson's catalyst in the presence of 1,4-diazabicyclo[2,2,2]octane to isomerize allyl group followed by deprotection with mercuric chloride and mercuric oxide (74%) [19] and acetylation with acetic anhydride in pyridine (96%). Reaction of **14** and **16** with potassium thioacetate in hexamethylphosphoric triamide (HMPA) gave the acetylated 5-thio derivatives **18** (67%) and **19** (63%), respectively.

Table 2
Nucleophilic substitution reaction of some 5-sulfonates with KSAc

Entry	Substrate	Solvent	Conditions	Yield [a]
1	**13**	DMF	r.t., 3 h	**17** 48%
2	**12**	DMF	70 °C, 1 day–80 °C, 2 days	N.R.
3	**11**	HMPA	85 °C, 3 h	**17** 74%
4	**14**	HMPA	90 °C, 5 h	**18** 67%
5	**16**	HMPA	80 °C, 6 h	**19** 63%

[a] Isolated yield. N.R. = no reaction.



Scheme 2. (i) TsCl, DMAP, pyridine. (ii) MsCl, pyridine. (iii) Tf_2O, pyridine, CH_2Cl_2, −20 °C. (iv) Pd–C, MeOH, reflux or $(Ph_3P)_3RhCl$, EtOH–PhH–H_2O, reflux. (v) $HgCl_2$, HgO, aq acetone. (vi) Ac_2O, pyridine. (vii) See Table 2. (viii) 70% AcOH, 70 °C. (ix) NaOMe. (x) aq NH_3, MeOH, DTT.

Conversion of the 5-thiofuranoses **17**, **18**, and **19** into the 5-thiopyranoses was performed as follows. As deacetylation before deisopropylidenation gave a disulfide, the isopropylidene acetal group of **17**, **18**, and **19** was first hydrolyzed in 70% aqueous acetic acid at 70 °C to give **20**, **21**, and **22**, respectively. Treatment of **20** with sodium methoxide in methanol gave a mixture of **23** and 4-acetate **24**, reacetylation of which furnished in a single product, 3-*O*-allyl-5-thio-L-fucopyranose triacetate (**25**, 86% from **17**). 5-Thio-L-fucopyranose (**26**), however, could not be obtained by similar deacetylation of **21** and **22**. Consequently, the acetyl group of **21** and **22** was removed by treatment with aqueous ammonia in methanol in the presence of DL-dithiothreitol. The 5-thio-L-fucopyranose thus obtained was characterized as its crystalline tetraacetate **27** (62% from **18**, 72% from **19**).

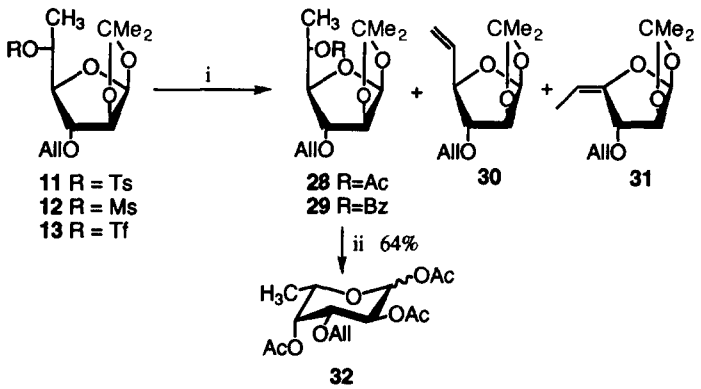
The 6-deoxy-D-altrofuranose derivative **9** would also be a useful intermediate for the synthesis of 3-*O*-substituted-L-fucose derivatives that are synthetic intermediates for a 3-*O*-glycosylated L-fucopyranosyl residue. Substitution of the three 5-sulfonates **11**, **12**, and **13** with three oxygen nucleophiles, namely NaOAc, NaOBz, and Bu_4NOAc was examined in two solvents, DMF and HMPA. The results are summarized in Table 3. Entries 3, 4, and 6, show that elimination products (**30** and **31**) were also obtained, along with the desired substitution products. The highest yield (75%) of the L-*galacto* isomer was attained by the reaction of 5-tosylate **11** with NaOBz in HMPA. Deacetylation or debenzoylation with sodium methoxide in methanol gave **10**. The isopropylidene acetal was hydrolyzed in 70% aqueous acetic acid at 70 °C, and subsequent acetylation gave 3-*O*-allyl-L-fucopyranose triacetate (**32**, 64% from **10**).

*Synthesis and inhibitory activity of 5-thio-*D*-arabinose.*—Acetylation of 5-*O*-trityl-D-arabinofuranose (**1**) with acetic anhydride in pyridine gave the triacetate **33** (94%) [20]

Table 3
Nucleophilic substitution reaction of some 5-sulfonates with some oxygen nucleophiles

Entry	Substrate	Nucleophile	Solvent	Conditions	Yield [a]
1	**13**	NaOAc	DMF	r.t., 1.5 h	**10** 63% (from **9**)
2	**12**	NaOBz	DMF	90 °C, 3 h	N.R.
3	**12**	Bu_4NOAc	DMF	70 °C, 5 h	**28** 60% Ene 28%
4	**12**	Bu_4NOAc	HMPA	85 °C, 9 h	**28** 47% Ene 8.3%
5	**11**	NaOAc	DMF	90 °C, 24 h	N.R.
6	**11**	NaOBz	HMPA	90 °C, 3 days	**29** 75% Ene 24%

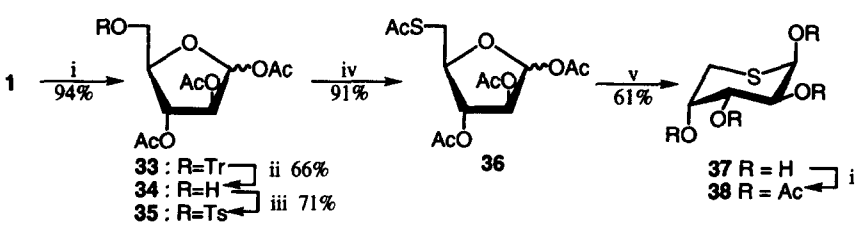
[a] Isolated yield. N.R. = no reaction. Ene = mixture of **30** and **31**.



Scheme 3. (i) See Table 3. (ii) 70% AcOH, 70 °C then Ac_2O, pyridine.

as an anomeric mixture ($\alpha:\beta = 2:1$). Detritylation of **33** with 80% aqueous acetic acid at 65 °C gave 1,2,3-tri-*O*-acetyl-D-arabinofuranose (**34**) [21] in 66% yield. Treatment of **34** with *p*-toluenesulfonyl chloride in pyridine gave the 5-tosylate **35** (71%). Substitution proceeded smoothly with KSAc in DMF to give the 5-thioacetate **36** (91%). The methyl signals of the acetylthio group ($\alpha:\delta$ 2.36, $\beta:\delta$ 2.35) in the ^1H NMR and C-5 signals in ^{13}C NMR at higher fields ($\alpha:\delta$ 30.9, $\beta:\delta$ 32.9) supports the structure assigned for **36**. Deacetylation with NaOMe in methanol gave crystalline 5-thio-D-arabinopyranose (**37**, 61%). Its peracetate **38** was identified by the ^1H NMR signals first reported by Hughes et al. [10].

The inhibitory activity of 5-thio-D-arabinose (**37**) against α-L-fucosidase from bovine



Scheme 4. (i) Ac_2O, pyridine. (ii) 60% AcOH, 65 °C. (iii) TsCl, pyridine. (iv) AcSK, DMF. (v) NaOMe.

kidney was measured by using *p*-nitrophenyl α-L-fucopyranoside as a substrate at pH 5.5. Based on a Lineweaver–Burk plot, **37** proved to be a competitive inhibitor and the K_i value, determined by a replot, was 0.77 mM, which is about 9 times larger than that of 5-thio-L-fucose (K_i = 0.084 mM) [1]. This difference of K_i values indicates that the α-L-fucosidase–5-thio-D-arabinose complex is destabilized by 1.4 kcal/mol in comparison with its 5-thio-L-fucose complex. Thus, the 6-methyl group in L-fucose is crucial for binding with α-L-fucosidase from bovine kidney.

3. Experimental

General procedures.—Melting points were determined with a Yanagimoto micro melting-point apparatus and were uncorrected. Optical rotations were measured on Jasco DIP-4 polarimeter in 0.5 dm cell. Column chromatography was performed with Silica Gel 60 (E. Merck, 7734, 70–230 mesh) or Wakogel C-300 (Wako Pure Chem. Ind., Ltd., 200–300 mesh). TLC was carried out on precoated plates Silica Gel 60 F254 (E. Merck, 5715), with detection by charring with 5% H_2SO_4–MeOH or 1% $Ce(SO_4)_2$–1.5% $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$–10% H_2SO_4. ^1H NMR spectra (90, 100 or 270 MHz) were recorded on a Jeol FX-90Q, PS-100 or EX-270 spectrometer. Chemical shifts were given in ppm measured downfield from internal Me_4Si, and spin–spin coupling constants are in Hz. ^{13}C NMR spectra were recorded on a Jeol FX-90Q or EX-270 spectrometer. *p*-Nitrophenyl α-L-fucopyranoside was purchased from Seikagaku Kogyo Co. Bovine kidney α-L-fucosidase was purchased from Sigma Chemical Co.

5-O-Triphenylmethyl-D-arabinofuranose (**1**).—A mixture of dry D-arabinose (12.9 g) and chlorotriphenylmethane (28.9 g) in pyridine (250 mL) was stirred vigorously for two days at room temperature. Then MeOH (42 mL) was added and the solvent was concentrated at 40 °C. From the residue was evaporated 3 times a 4:1 (v/v) mixture of toluene–EtOH (55 mL) and the product was dissolved in $CHCl_3$. The solution was washed with 0.5 M HCl, water and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (5:4 hexane–EtOAc and then 9:1 EtOAc–MeOH) to give amorphous **1** (21.5 g, 64%) whose physical data were identical with those reported [12].

1,2-O-Isopropylidene-5-O-triphenylmethyl-β-D-arabinofuranose (**2**).—A mixture of **1** (1.27 g), 2,2-dimethoxypropane (6.4 mL), and *p*-toluenesulfonic acid monohydrate (4.7 mg) in acetone (6.4 mL) was stirred for 90 min at room temperature. Methanol (2.6 mL) was added and TLC indicated the disappearance of a faster-moving product. The solution was diluted with $CHCl_3$, neutralized with satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (3:2 hexane–EtOAc) to give syrupy **2** (1.00 g, 72%); $[\alpha]_D^{21}$ −1.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.46–7.20 (m, 15 H, Tr), 5.88 (d, 1 H, $J_{1,2}$ 4.3 Hz, H-1), 4.51 (d, 1 H, H-2), 4.34 (brd, 1 H, H-3), 4.14 (ddd, 1 H, $J_{3,4}$ 2.3, $J_{4,5a}$ 5.6, $J_{4,5b}$ 7.6 Hz, H-4), 3.41 (dd, 1 H, $J_{5a,5b}$ 9.2 Hz, H-5a), 3.25 (dd, 1 H, H-5b), 1.25, 1.17 (each s, 3 H × 2, CMe_2); ^{13}C NMR ($CDCl_3$) δ 143.8, 128.7–127.0 (Tr), 112.4 (CMe_2), 105.6 (C-1), 86.9, 86.6, 76.6 (C-2, 3, 4), 63.9 (C-5), 26.6, 26.1 (CMe_2). Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 75.22; H, 6.81.

3-O-Allyl-1,2-O-isopropylidene-5-O-triphenylmethyl-β-D-arabinofuranose (**3**).—To an ice-cold solution of **2** (0.550 g) in DMF (2.4 mL) was added NaH (55%, 0.112 g), and the mixture was stirred for 30 min at room temperature. Allyl bromide (0.22 mL) was then added dropwise at 0 °C, and after stirring for 30 min at room temperature, MeOH was added at 0 °C to decompose the excess reagent. The reaction mixture was poured into 2:1 (v/v) EtOAc–brine (18 mL), and the organic layer was washed 6 times with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (8:1 hexane–EtOAc) to give syrupy **3** (0.461 g, 77%); $[\alpha]_D^{21}$ −6.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.47–7.19 (m, 15 H, Tr), 5.98–5.83 (m, 1 H, All), 5.86 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.34–5.19 (m, 2 H, All), 4.55 (d, 1 H, H-2), 4.25 (ddd, 1 H, $J_{3,4}$ 2.3, $J_{4,5a}$ 5.3, $J_{4,5b}$ 7.6 Hz, H-4), 4.13–4.08 (m, 3 H, H-3, All), 3.37 (dd, 1 H, $J_{5a,5b}$ 9.2 Hz, H-5a), 3.22 (dd, 1 H, H-5b), 1.25, 1.18 (each s, 3 H × 2, CMe_2); ^{13}C NMR ($CDCl_3$) δ 143.9, 128.7–127.0 (Tr), 134.0 (All), 117.5 (All), 112.3 (CMe_2), 105.8 (C-1), 84.9, 84.3, 83.1 (C-2, 3, 4), 70.6 (All), 63.6 (C-5), 26.6, 26.1 (CMe_2). Anal. Calcd for $C_{30}H_{32}O_5$: C, 76.25; H, 6.83. Found: C, 75.86; H, 6.44.

3-O-Allyl-1,2-O-isopropylidene-β-D-arabinofuranose (**4**).—(*a*) A mixture of **3** (0.247 g), 2,2-dimethoxypropane (1.5 mL) and *p*-toluenesulfonic acid monohydrate (0.010 g) in $CHCl_3$ (1.5 mL) was stirred overnight at room temperature. The mixture was neutralized with satd aq $NaHCO_3$ and extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated. The residue was dissolved in glacial AcOH (TLC indicated the disappearance of faster-moving product) and then concentrated, with evaporation of toluene. The residue was chromatographed on silica gel (8:1 hexane–EtOAc and then 3:2 hexane–EtOAc then EtOAc) to give syrupy **4** (0.106 g, 88%).

(*b*) A mixture of **3** (0.159 g) in formic acid (0.98 mL) and ether (0.63 mL) was stirred for 5 min, diluted with $CHCl_3$, washed with water and satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. Column chromatography (6:1 hexane–EtOAc then 1:1 hexane–EtOAc) afford syrupy **4** (0.049 g, 64%); $[\alpha]_D^{21}$ +21.4° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.97–5.83 (m, 1 H, All), 5.90 (d, 1 H, $J_{1,2}$ 4.3 Hz, H-1), 5.34–5.21 (m, 2 H, All), 4.62 (d, 1 H, H-2), 4.16 (dd, 1 H, $J_{4,5}$ 5.6 Hz, H-4), 4.13–4.00 (m, 2 H, All), 3.92 (d, 1 H, $J_{3,4}$ 3.3 Hz, H-3), 3.76 (t, 2 H, $J_{5,OH}$ 5.6 Hz, H-5a,b), 2.17 (t, 1 H, OH-5), 1.53, 1.34 (each s, 3 H × 2, CMe_2); ^{13}C NMR ($CDCl_3$) δ 133.8 (All), 117.7 (All), 112.8 (CMe_2), 105.6 (C-1), 85.7, 85.2, 82.8 (C-2, 3, 4), 70.8 (All), 62.7 (C-5), 27.1, 26.3 (CMe_2). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.48; H, 8.09.

Synthesis of **4** *from* D-*arabinose diethyl dithioacetal* (**5**).—To mixture of **5** (4.11 g) in pyridine (48 mL) was added BzCl (2.25 g) dropwise for 15 min at −15 °C. After stirring for 2.5 h, the mixture was poured into 10% aq AcOH (320 mL) and the precipitate was filtered off. To the mother liquor was added 5% aq AcOH (160 mL) and additional precipitate was filtered off. The combined precipitate was recrystallized from $CHCl_3$–hexane to give 5-*O*-benzoyl-D-arabinose diethyl dithioacetal (**6**, 4.72 g, 82%); mp 119–121 °C; $[\alpha]_D^{26}$ −53.6° (*c* 1.0, $CHCl_3$), lit. [14] mp 118.5–119.5 °C; $[\alpha]_D$ −48° (*c* 0.073, $CHCl_3$).

A mixture of **6** (60.0 g), anhydrous $CuSO_4$ (32.9 g) and $HgCl_2$ (100 g) in dry acetone (414 mL) was stirred for 30 min at room temperature. The precipitate was filtered off and the mother liquor was neutralized with Et_3N and concentrated. The residue was

dissolved in $CHCl_3$ and washed with aq KI, dried ($MgSO_4$), and concentrated. The residue was crystallized from EtOAc–ether to give 5-*O*-benzoyl-1,2-*O*-isopropylidene-β-D-arabinofuranose (**7**, 31.0 g, 63%). The remaining syrupy was chromatographed on silica gel (3:2 hexane–EtOAc) to give additional **7** (5.10 g, 10%); mp 147–149 °C; $[\alpha]_D^{26}$ +21.7° (*c* 1.0, $CHCl_3$), lit. [14] mp 147.5–148.5 °C; $[\alpha]_D$ +25.25° (*c* 0.079, $CHCl_3$).

A mixture of **7** (0.302 g) and NaH (55%, 0.058 g) in DMF (15 mL) under an Ar atmosphere was stirred for 15 min at 0 °C. Allyl bromide (0.17 mL) was added dropwise, and stirring was continued for 25 min at 0 °C. Methanol (0.5 mL) was added dropwise with stirring at room temperature, and then 0.5 M methanolic NaOMe (1 mL) was added to complete the reaction. The mixture was diluted with EtOAc, washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (6:1 then 1:1 hexane–EtOAc) to give syrupy **4** (0.172 g, 73%).

3-O-Allyl-1,2-O-isopropylidene-β-D-arabino-pentodialdo-1,4-furanose (**8**).—To a stirring solution of $(COCl)_2$ (1.10 g) in CH_2Cl_2 (17.3 mL) was added dropwise a solution of Me_2SO (0.95 g) in CH_2Cl_2 (17.3 mL) at −78 °C. After stirring for 5 min, a solution of **4** (0.50 g) in CH_2Cl_2 (6.5 mL) was added dropwise, with stirring at −78 °C for 15 min. Triethylamine (2.4 mL) was added and after 5 min, the reaction mixture was allowed to attain room temperature, and poured into satd aq $NaHCO_3$, extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (50:1 then 1:1 hexane–EtOAc) to give syrupy **8** (0.46 g, 93%); ^1H NMR ($CDCl_3$) δ 9.77 (s, 1 H, H-5), 6.05 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.96–5.82 (m, 1 H, All), 5.36–5.22 (m, 2 H, All), 4.58 (d, 1 H, H-2), 4.47 (s, 1 H, H-4), 4.25 (s, 1 H, H-3), 4.09, 4.07 (m, 2 H, All), 1.43, 1.30 (each s, 3 H × 2, CMe_2); ^{13}C NMR ($CDCl_3$) δ 201.7 (C-5), 133.3 (All), 118.2 (All), 112.1 (CMe_2), 106.6 (C-1), 88.8, 84.6, 82.8 (C-2, 3, 4), 70.8 (All), 26.1, 25.6 (CMe_2).

Nucleophilic addition reaction to 3-O-allyl-1,2-O-isopropylidene-β-D-arabino-pentodialdo-1,4-furanose (**8**).—*(a) [Entry 6, Table 1]* To a solution of **8** (1.24 g) in ether was added dropwise a solution of MeLi in ether (1.15 M, 37.5 mL) at −78 °C, with stirring for 30 min under Ar atmosphere. Saturated aq NH_4Cl was added and the mixture was extracted with ether, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (2:1 hexane–EtOAc) to give 3-*O*-allyl-6-deoxy-1,2-*O*-isopropylidene-β-D-altrofuranose (**9**) and 3-*O*-allyl-6-deoxy-1,2-*O*-isopropylidene-α-L-galactofuranose (**10**) (1.02 g, 77%).

(b) [Entry 9, Table 1] To a solution of **8** (0.901 g) in CH_2Cl_2 was added dropwise a solution of Me_3Al in hexane (2.0 M, 6.64 mL) at −70 °C, and allowed to −10 °C with stirring for 240 min. Methanol was added and the solution was diluted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated. The residue, purified for as entry 6, gave **9** and **10** (0.630 g, 65%).

Purification of **9**.—A mixture of **9** and **10** was acetylated with Ac_2O in pyridine, and chromatographed on silica gel (3:1 CH_2Cl_2–toluene). Deacetylation of the faster-moving material (56.9 mg) with 0.1 M methanolic NaOMe gave **9** (22.4 mg, 49%) as a single isomer; **9** $[\alpha]_D^{21}$ +8.9° (*c* 1.0, $CHCl_3$); ^1H NMR (acetone-d_6) δ 5.98–5.84 (m, 1 H, All), 5.83 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-1), 5.33–5.11 (m, 2 H, All), 4.60 (d, 1 H, H-2), 4.13 (d, 1 H, $J_{3,4}$ 1.8 Hz, H-3), 4.08–4.06 (brd, 2 H, All), 3.94–3.85 (m, 2 H, H-5,

OH-5), 3.68 (dd, 1 H, $J_{4,5}$ 7.9 Hz, H-4), 1.43, 1.27 (each s, 3 H × 2, CMe_2), 1.19 (d, 3 H, $J_{5,6}$ 5.9 Hz, H-6); ^{13}C NMR ($CDCl_3$) δ 133.9 (All), 117.6 (All), 112.8 (CMe_2), 105.3 (C-1), 89.2, 85.5, 82.2 (C-2, 3, 4), 70.6 (All), 67.0 (C-5), 27.2, 26.4 (CMe_2), 19.6 (C-6). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.54; H, 8.43.

3-O-Allyl-6-deoxy-1,2-O-isopropylidene-5-O-p-toluenesulfonyl-β-D-altrofuranose (**11**).—A mixture of **9** (1.04 g), *p*-toluenesulfonyl chloride (1.39 g) and catalytic amount of 4-dimethylaminopyridine in pyridine (3.5 mL) was stirred for two days at room temperature, and then satd aq $NaHCO_3$ and $CHCl_3$ were added. The organic layer was washed with 2.4 M HCl and water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (2:1 hexane–EtOAc) to give syrupy **11** (1.47 g, 86%, D-*altro*:L-*galacto* = 89:11); ^1H NMR ($CDCl_3$) δ 7.80, 7.35 (each d, 2H × 2, *J* 8.3 Hz, Ts-Ar), 5.91–5.76 (m, 1 H, All), 5.85 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.30–5.16 (m, 2 H, All), 4.82 (dq, 1 H, $J_{5,6}$ 6.6 Hz, H-5), 4.52 (d, 1 H, H-2), 3.99–3.94 (m, 3 H, H-3, All), 3.88 (dd, 1 H, $J_{3,4}$ 1.7, $J_{4,5}$ 8.9 Hz, H-4), 2.46 (s, 3 H, Ts-Me), 1.49, 1.30 (each s, 3 H × 2, CMe_2), 1.32 (d, 3 H, H-6); ^{13}C NMR ($CDCl_3$) δ 144.8, 133.5, 129.8, 127.9 (Ts-Ar), 134.2 (All), 117.8 (All), 112.4 (CMe_2), 106.1 (C-1), 86.4, 84.4, 82.1 (C-2, 3, 4), 70.5 (All), 78.0 (C-5), 26.8, 25.8 (CMe_2), 21.6 (Ts-Me), 17.7 (C-6). Anal. Calcd for $C_{19}H_{26}O_7S$: C, 57.27; H, 6.58; S, 8.05. Found: C, 57.35; H, 6.77; S, 7.66.

3-O-Allyl-6-deoxy-1,2-O-isopropylidene-5-O-methanesulfonyl-β-D-altrofuranose (**12**).—A mixture of **9** (0.164 g) and methanesulfonyl chloride (0.103 mL) in pyridine (3.3 mL) was stirred overnight at room temperature. The solution was diluted with $CHCl_3$, washed with satd aq $NaHCO_3$, M HCl and water, dried ($MgSO_4$), and concentrated to give syrupy **12** (0.213 g, 98%); ^1H NMR ($CDCl_3$) δ 5.97–5.83 (m, 1 H, All), 5.88 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.36–5.22 (m, 2 H, All), 4.93 (dq, 1 H, H-5), 4.61 (d, 1 H, H-2), 4.15–4.00 (m, 3 H, H-3, All), 3.93 (dd, 1 H, $J_{3,4}$ 3.0, $J_{4,5}$ 7.6 Hz, H-4), 3.05 (s, 3 H, Ms), 1.59, 1.33 (each s, 3 H × 2, CMe_2), 1.51 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6).

6-Deoxy-1,2-O-isopropylidene-3-O-(prop-1-enyl)-5-O-p-toluenesulfonyl-β-D-altrofuranose (**14**).—A mixture of **11** (2.34 g) and 5% Pd–C (9.13 g) in MeOH (34.4 mL) was stirred for 6.5 h at 50 °C. The solution was diluted with EtOAc, filtered through Celite, and concentrated to give syrupy **14** (2.09 g, 98%); ^1H NMR ($CDCl_3$) δ 7.83–7.79, 7.37–7.34 (each m, 2 H × 2, Ts-Ar), 6.03–5.98 (m, Pre(*E*)), 5.89 (d, $J_{1,2}$ 4.0 Hz, H-1(*Z*)), 5.84 (d, $J_{1,2}$ 4.0 Hz, H-1(*E*)), 5.84–5.81 (m, Pre(*Z*)), 4.90–4.76 (m, H-5, Pre(*E*)), 4.59–4.49 (m, H-2, Pre(*Z*)), 4.16 (brd, 1 H, H-3), 3.91 (brd, 1 H, H-4), 2.46 (s, 3 H, Ts-Me), 1.55–1.51 (m, 6 H, CMe_2, Pre), 1.35 (d, $J_{5,6}$ 6.3 Hz, H-6(*E*)), 1.33 (d, $J_{5,6}$ 6.3 Hz, H-6(*Z*)), 1.29 (s, 3 H, CMe_2).

*6-Deoxy-1,2-O-isopropylidene-5-O-p-toluenesulfonyl-β-D-*altrofuranose (**15**).—A mixture of **11** (2.90 g), tris(triphenylphosphine)rhodium(I) chloride (0.509 g) and 1,4-diazabicyclo[2,2,2]octane (2.44 g) in 7:3:1 (v/v/v) EtOH–benzene–water (120 mL) was boiled for 2.5 h under reflux. The solvent was removed and the residue was dissolved in $CHCl_3$. The solution was washed with water, M HCl, satd aq $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. A mixture of the residue, $HgCl_2$ (3.05 g, 11.22 mmol) and HgO (2.46 g, 11.37 mmol) in 4:1 (v/v) acetone–water (82 mL) was stirred overnight at room temperature. The precipitate was filtered off, and the filtrate was concentrated. The residue was dissolved in $CHCl_3$, the solution was washed with water, aq KI and water, dried ($MgSO_4$), and concentrated. The residue was chromatographed

on silica gel (1:1 hexane–EtOAc) to give **15** (1.97 g, 74%). An analytical sample recrystallized from ether had mp 105–107 °C; $[\alpha]_D^{23}$ +9.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.80, 7.35 (each d, 2 H × 2, *J* 8.1 Hz, Ts-Ar), 5.88 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.85 (dq, 1 H, $J_{5,6}$ 6.4 Hz, H-5), 4.50 (d, 1 H, H-2), 4.32 (brd, 1 H, H-3), 3.83 (dd, 1 H, $J_{3,4}$ 1.7, $J_{4,5}$ 9.2 Hz, H-4), 2.51 (d, 1 H, $J_{3,OH}$ 4.6 Hz, OH-3), 2.46 (s, 3 H, Ts-Me), 1.48, 1.29 (each s, 3 H × 2, CMe_2), 1.30 (d, 3 H, H-6); ^{13}C-NMR ($CDCl_3$) δ 145.0, 134.0, 129.9, 127.8 (Ts-Ar), 112.5 (CMe_2), 105.9 (C-1), 88.7, 86.5, 78.2, 75.5 (C-2, 3, 4, 5), 26.7, 25.8 (CMe_2), 21.7 (Ts-Me), 17.7 (C-6). Anal. Calcd for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19. Found: C, 53.97; H, 6.10.

3-O-Acetyl-6-deoxy-1,2-O-isopropylidene-5-O-p-toluenesulfonyl-β-D-altrofuranose (**16**).—The 5-tosylate **15** (1.59 g) was acetylated with Ac_2O in pyridine to give syrupy **16** (1.70 g, 96%); $[\alpha]_D^{23}$ −3.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.83, 7.35 (each d, 2 H × 2, *J* 8.2 Hz, Ts-Ar), 5.86 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.02 (d, 1 H, $J_{3,4}$ 1.3 Hz, H-3), 4.86 (dq, 1 H, $J_{4,5}$ 9.2 Hz, $J_{5,6}$ 6.3 Hz, H-5), 4.46 (d, 1 H, H-2), 3.90 (brd, 1 H, H-4), 2.45 (s, 3 H, Ts-Me), 2.05 (s, 3 H, Ac), 1.50, 1.27 (each s, 3 H × 2, CMe_2), 1.39 (d, 3 H, H-6); ^{13}C NMR ($CDCl_3$) δ 169.3 (C=O), 144.9, 133.7, 129.9, 128.0 (Ts-Ar), 112.7 (CMe_2), 106.0 (C-1), 86.3, 84.2, 77.1, 76.6 (C-2, 3, 4, 5), 26.6, 25.7 (CMe_2), 21.7 (Ts-Me), 20.8 (Ac), 17.7 (C-6). Anal. Calcd for $C_{18}H_{24}O_8S$: C, 53.99; H, 6.04. Found: C, 54.47; H, 6.19.

5-S-Acetyl-3-O-allyl-6-deoxy-1,2-O-isopropylidene-5-thio-α-L-galactofuranose (**17**).—A mixture of **11** (1.11 g) and KSAc (0.964 g) in HMPA (11 mL) was stirred for 3 h at 85 °C. The solution was cooled and poured into 2:1 (v/v) EtOAc–water, washed 4 times with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (8:1 hexane–EtOAc) to give syrupy **17** (0.628 g, 74%, L-*galacto*:D-*altro* = 91:9); ^{1}H NMR ($CDCl_3$) δ 5.97–5.83 (m, 1 H, All), 5.77 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.35–5.20 (m, 2 H, All), 4.56 (dd, 1 H, $J_{2,3}$ 1.3 Hz, H-2), 4.16–3.97 (m, 2 H, All), 3.94–3.85 (m, 2 H, H-4, H-5), 3.78 (dd, 1 H, $J_{3,4}$ 5.1 Hz, H-3), 2.34 (s, 3 H, SAc), 1.58, 1.35 (each s, 3 H × 2, CMe_2), 1.41 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6); ^{13}C NMR ($CDCl_3$) δ 195.1 (SAc), 133.9 (All), 117.9 (All), 114.1 (CMe_2), 104.7 (C-1), 85.9, 85.2, 83.9 (C-2, 3, 4), 71.2 (All), 41.4 (C-5), 30.8 (SAc), 27.6, 27.0 (CMe_2), 19.6 (C-6). Anal. Calcd for $C_{14}H_{22}O_5S$: C, 55.61; H, 7.33; S, 10.60. Found: C, 55.62; H, 7.35; S, 10.77.

5-S-Acetyl-6-deoxy-1,2-O-isopropylidene-3-O-(prop-1-enyl)-5-thio-α-L-galactofuranose (**18**).—Reaction of **14** (0.754 g) with KSAc (1.08 g) in HMPA (7.4 mL) was performed at 90 °C for 5 h. Chromatography on silica gel (9:1 hexane–EtOAc) gave syrupy **18** (0.384 g, 67%); ^{1}H NMR ($CDCl_3$) δ 6.19–6.13 (m, Pre(*E*)), 6.00–5.96 (m, Pre(*Z*)), 5.81 (d, $J_{1,2}$ 4.0 Hz, H-1(*Z*)), 5.76 (d, $J_{1,2}$ 4.0 Hz, H-1(*E*)), 5.01–4.89 (m, Pre(*E*)), 4.63–4.52 (m, H-2, Pre(*Z*)), 4.18–3.87 (m, 3 H, H-3, 4, 5), 2.35 (s, 3 H, SAc), 1.61–1.54 (m, 6 H, CMe_2, Pre), 1.42 (d, $J_{5,6}$ 6.9 Hz, H-6(*Z*)), 1.41 (d, $J_{5,6}$ 6.6 Hz, H-6(*E*)), 1.36, 1.34 (each s, 3 H, CMe_2).

3-O-Acetyl-5-S-acetyl-6-deoxy-1,2-O-isopropylidene-5-thio-α-L-galactofuranose (**19**).—Reaction of **16** (1.70 g) with KSAc (1.46 g) in HMPA (16.8 mL) was performed at 80 °C for 6 h. Chromatography on silica gel (2:1 hexane–EtOAc) gave syrupy **19** (0.809 g, 63%); $[\alpha]_D^{21}$ −7.4° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.83 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.06 (d, 1 H, $J_{3,4}$ 3.6 Hz, H-3), 4.56 (d, 1 H, H-2), 3.99 (dd, 1 H, $J_{4,5}$ 6.9 Hz, H-4), 3.92 (qu, 1 H, $J_{5,6}$ 6.9 Hz, H-5), 2.34 (s, 3 H, SAc), 2.10 (s, 3 H, OAc), 1.60, 1.34

(each s, 3 H × 2, CMe_2), 1.43 (d, 3 H, H-6); ^{13}C NMR ($CDCl_3$) δ 194.8 (SC=O), 169.8 (OC=O) 114.0 (CMe_2), 105.0 (C-1), 85.3, 85.3, 77.6 (C-2, 3, 4), 41.5 (C-5), 30.8 (SAc), 27.6, 26.5 (CMe_2), 20.8 (OAc), 19.3 (C-6). Anal. Calcd for $C_{13}H_{20}O_6S$: C, 51.30; H, 6.62; S, 10.54. Found: C, 51.15; H, 6.52; S, 10.76.

3-O-Allyl-1,2,4-tri-O-acetyl-5-thio-α-L-fucopyranose (**25**).—A solution of **17** (0.159 g) in 70% aq AcOH was stirred for 2 h at 90 °C and then concentrated and toluene evaporated from the residue. The residue containing 5-*S*-acetyl-3-*O*-allyl-6-deoxy-L-galactofuranose (**20**) was dissolved in 0.1 M methanolic NaOMe (19.2 mL), TLC indicated the disappearance of **20**. The solution was neutralized with Amberlite IR-120B (H^+), the resin was filtered off, and the filtrate was concentrated. The residue was acetylated with Ac_2O in pyridine and chromatographed on silica gel (2:1 hexane–EtOAc) to give **25** (0.156 g, 86%). An analytical sample recrystallized from ether–petroleum ether had mp 108–110 °C; $[\alpha]_D^{23}$ −301° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.07 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 5.91–5.76 (m, 1 H, All), 5.60 (dd, 1 H, $J_{4,5}$ 1.7 Hz, H-4), 5.37 (dd, 1 H, $J_{2,3}$ 10.4 Hz, H-2), 5.30–5.15 (m, 2 H, All), 4.17–3.95 (m, 2 H, All), 3.75 (dd, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 3.52 (dq, 1 H, $J_{5,6}$ 7.3 Hz, H-5), 2.18, 2.15, 2.03 (each s, 3 H × 3, Ac × 3), 1.18 (d, 3 H, H-6); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.0, 169.3 (C=O), 134.4 (All), 117.1 (All), 74.7 (C-1), 72.6, 71.8, 71.0 (C-2, 3, 4), 71.1 (All), 36.0 (C-5), 21.0, 20.9 (Ac), 16.1 (C-6). Anal. Calcd for $C_{15}H_{22}O_7S$: C, 52.01; H, 6.40; S, 9.26. Found: C, 52.14; H, 6.43; S, 9.42.

1,2,3,4-Tetra-O-acetyl-5-thio-α-L-fucopyranose (**27**).—[From **18**] A solution of **18** (0.384 g) in 70% aq AcOH (25 mL) was stirred at 70 °C. After the disappearance of **18** on TLC, the mixture was concentrated, and toluene evaporated from the residue. The residue containing 5-*S*-acetyl-6-deoxy-5-thio-L-galactofuranose (**21**) along in the DL-dithiothreitol were dissolved in MeOH (2 mL) and aq NH_3 (6 mL), stirred for 20 min, and then concentrated. The residue containing 5-thio-L-fucose (**26**) was acetylated with Ac_2O in pyridine, and chromatographed on silica gel (3:2 hexane–EtOAc) to give **27** (0.274 g, 62%) which was recrystallized from EtOH–petroleum ether.

[From **19**] A solution of **19** (0.809 g) in 70% aq AcOH (50 mL) was stirred for 3.5 h at 70 °C and concentrated (evaporated of toluene). The residue containing 3-*O*-acetyl-5-*S*-acetyl-6-deoxy-5-thio-L-galactofuranose (**22**) and DL-dithiothreitol (0.0423 g) were dissolved in methanol (8 mL) and aq NH_3 (12 mL), stirred for 30 min, and then the solvent was removed. The residue containing 5-thio-L-fucose (**26**) was acetylated with Ac_2O in pyridine, and chromatographed on silica gel (3:2 hexane–EtOAc). Recrystallization from EtOH–petroleum ether gave **27** (0.453 g, 49%). The mother liquor gave a further crop of **27** (0.212 g, 23%) after chromatography; mp 132–133 °C (from EtOH–petroleum ether); $[\alpha]_D^{21}$ −268° (*c* 1.0, $CHCl_3$); lit. [1] mp 132–133 °C; $[\alpha]_D^{23}$ −269.2° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.11 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 5.55 (dd, 1 H, $J_{4,5}$ 1.6 Hz, H-4), 5.46 (dd, 1 H, $J_{2,3}$ 10.9 Hz, H-2), 5.31 (dd, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 3.64 (dq, 1 H, $J_{5,6}$ 6.9 Hz, H-5), 2.19, 2.16, 2.02, 2.00 (each s, 3 H × 4, Ac × 4), 1.16 (d, 3 H, H-6). Anal. Calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; S, 9.20. Found: C, 48.42; H, 5.81; S, 9.31.

Nucleophilic substitution reaction with oxygen nucleophiles.—(*a*) [*Entry 1, Table 3*] To a solution of pyridine (97 μL) in CH_2Cl_2 (2 mL) was added dropwise a solution of Tf_2O (0.269 g) in CH_2Cl_2 (4.9 mL) at −20 °C under Ar with stirring for 30 min. A

solution of **9** (0.139 g) in CH_2Cl_2 (1.5 mL) was added dropwise with stirring for 30 min. The solution was washed with satd aq $NaHCO_3$, M HCl and water, dried ($MgSO_4$), and concentrated to give syrupy **13**. A mixture of **13** dried under high vacuum and NaOAc (0.258 g) in DMF (2 mL) was stirred for 1.5 h at room temperature, and concentrated. The residue was dissolved in $CHCl_3$, washed with water, dried ($MgSO_4$), and concentrated. The residue was treated with 0.1 M methanolic NaOMe, and chromatographed on silica gel (2:1 hexane–EtOAc) to give syrupy 3-*O*-allyl-6-deoxy-1,2-*O*-isopropylidene-α-L-galactofuranose **10** (0.0882 g, 63%).

(*b*) [*Entry 3, Table 3*] A mixture of **12** (91.2 mg) and Bu_4NOAc (0.180 g) in DMF (1.3 mL) was stirred for 4.5 h at 90 °C, and concentrated. The residue was dissolved in CH_2Cl_2 and washed twice with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (3:1 hexane–EtOAc) first to give a mixture of **30** and **31** (18.2 mg, 28%) and then 5-*O*-acetyl-3-*O*-allyl-6-deoxy-1,2-*O*-isopropylidene-α-L-galactofuranose **28** (48.6 mg, 60%). The 5-acetate **28** was deacetylated as described in (*a*) to give **10**.

(*c*) [*Entry 4, Table 3*] Reaction of **12** (0.177 g) with Bu_4NOAc (0.420 g) in HMPA (2.2 mL) was performed at 85 °C overnight. Work up as for entry 3 gave 5-*O*-acetyl-3-*O*-allyl-6-deoxy-1,2-*O*-isopropylidene-α-L-galactofuranose **28** (L-*galacto*:D-*altro* = 95:5) (0.0739 g, 47%) and mixture of **30** and **31** (0.0103 g, 8.3%). The 5-acetate **28** was deacetylated as described in (*a*) to give **10**.

(*d*) [*Entry 6, Table 3*] Reaction of **11** (98.5 mg) with NaOBz (0.180 g) in HMPA (1.1 mL) was performed for two days at 90 °C. Fractionation of the products by chromatography on silica gel (3:1 hexane–EtOAc) gave 3-*O*-allyl-5-*O*-benzoyl-6-deoxy-1,2-*O*-isopropylidene-α-L-galactofuranose **29** (64.5 mg, 75%) and a mixture of **30** and **31** (13.5 mg, 24%). 5-Benzoate **29** was debenzoylated as described in (*a*) to give **10**.

Data for **10**; $[\alpha]_D^{21}$ +20.2° (*c* 1.1, $CHCl_3$); ^{1}H NMR (acetone-d_6) δ 5.99–5.85 (m, 1 H, All), 5.84 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-1), 5.34–5.14 (m, 2 H, All), 4.64 (d, 1 H, H-2), 4.09–4.02 (m, 2 H, All), 3.88–3.79 (m, 2 H, H-3, 5), 3.67 (dd, 1 H, *J* 3.6, *J* 7.3 Hz, H-4), 3.37 (d, 1 H, $J_{5,OH}$ 3.6 Hz, OH-5), 1.46, 1.29 (each s, 3 H × 2, CMe_2), 1.14 (d, 3 H, $J_{5,6}$ 6.3 Hz, H-6); ^{13}C NMR ($CDCl_3$) δ 133.7 (All), 118.0 (All), 112.7 (CMe_2), 105.5 (C-1), 89.9, 85.1, 83.6 (C-2, 3, 4), 70.6 (All), 67.2 (C-5), 27.2, 26.2 (CMe_2), 19.0 (C-6). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.10; H, 8.01.

^{1}H NMR data for **28** ($CDCl_3$) δ 5.96–5.82 (m, 1 H, All), 5.83 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.34–5.22 (m, 2 H, All), 5.12 (qu, 1 H, $J_{5,6}$ 6.4 Hz, H-5), 4.57 (d, 1 H, H-2), 4.16–3.98 (m, 2 H, All), 3.88 (dd, 1 H, $J_{4,5}$ 6.4 Hz, H-4), 3.79 (d, 1 H, $J_{3,4}$ 4.8 Hz, H-3), 2.07 (s, 1 H, Ac), 1.57, 1.36 (each s, 3 H × 2, CMe_2), 1.29 (d, 3 H, H-6); ^{13}C NMR ($CDCl_3$) δ 170.4 (C=O), 133.6 (All), 118.0 (All), 113.7 (CMe_2), 105.0 (C-1), 85.4, 85.2, 82.7 (C-2, 3, 4), 70.9 (All), 69.6 (C-5), 27.3, 26.8 (CMe_2), 21.3 (Ac), 16.9 (C-6); Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.75; H, 7.48.

^{1}H NMR data for **29** ($CDCl_3$) δ 8.13–8.05 (m, 2 H, Bz), 7.65–7.39 (m, 3 H, Bz), 5.96–5.81 (m, 1 H, All), 5.85 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.40 (qu, 1 H, $J_{5,6}$ 6.3 Hz, H-5), 5.34–5.19 (m, 2 H, All), 4.60 (dd, 1 H, $J_{2,3}$ 1.3 Hz, H-2), 4.18–4.01 (m, 2 H, All), 4.03 (dd, 1 H, $J_{4,5}$ 6.3 Hz, H-4), 3.90 (dd, 1 H, $J_{3,4}$ 5.0 Hz, H-3), 1.58, 1.35 (each s, 3 H × 2, CMe_2), 1.42 (d, 3 H, H-6).

^{1}H NMR data for **30** and **31** ($CDCl_3$) δ 6.06 (m, H-5 **30**), 6.00 (d, $J_{1,2}$ 3.0 Hz, H-1

31), 5.89 (d, $J_{1,2}$ 4.1 Hz, H-1 **30**), 5.97–5.81 (m, All), 5.34 (m, H-6a,b **30**), 5.29–5.12 (m, All), 5.17 (q, $J_{5,6}$ 6.4 Hz, H-5 **31**), 4.59 (d, H-2 **30**), 4.58 (d, H-2 **31**), 4.51 (s, H-3 **31**), 4.47 (m, H-4 **30**), 4.15–3.98 (m, All), 3.87 (d, $J_{3,4}$ 2.9 Hz, H-3 **30**), 1.68 (d, H-6 **31**), 1.52, 1.44, 1.36, 1.33 (each s, CMe_2).

3-O-Allyl-1,2,4-tri-O-acetyl-L-fucopyranose (**32**).—A solution of **10** (20.0 mg) in 70% aq AcOH was stirred for 2 h at 70 °C, and concentrated (toluene). The residue was acetylated with Ac_2O in pyridine, and chromatographed on silica gel (3:2 hexane–EtOAc) to give **32** (17.4 mg, 64%, $\alpha:\beta = 8:92$); ^{1}H NMR data of the β anomer ($CDCl_3$) δ 5.84–5.72 (m, 1 H, All), 5.63 (d, 1 H, $J_{1,2}$ 8.6 Hz, H-1), 5.29 (d, 1 H, H-4), 5.27–5.15 (m, 2 H, All), 5.22 (dd, 1 H, $J_{2,3}$ 10.1 Hz, H-2), 4.17–3.88 (m, 2 H, All), 3.84 (q, 1 H, $J_{5,6}$ 6.6 Hz, H-5), 3.58 (dd, 1 H, $J_{3,4}$ 3.5 Hz, H-3), 2.18, 2.11, 2.07 (each s, 3 H × 3, Ac × 3), 1.23 (d, 3 H, H-6); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.0, 169.3 (C=O), 134.4 (All), 117.1 (All), 74.7 (C-1), 72.6, 71.8, 71.0 (C-2, 3, 4), 71.1 (All), 36.0 (C-5), 21.0, 20.9 (Ac), 16.1 (C-6); Anal. Calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.71. Found: C,54.67; H, 6.81.

Synthesis of 5-thio-D-arabinopyranose tetraacetate (**37**).—A solution of **1** (1.42 g) in Ac_2O (2.4 mL) and pyridine (4.8 mL) was stirred for 12.5 h at room temperature, then MeOH was added and the solution concentrated. The residue was dissolved in $CHCl_3$ and washed with M HCl, satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated to give syrupy 1,2,3-tri-*O*-acetyl-5-*O*-triphenylmethyl-D-arabinofuranose (**33**, 1.77 g, 94%); ^{1}H NMR ($CDCl_3$) δ 7.49–7.17 (m, 15 H, Tr), 6.35 (d, $J_{1,2}$ 5.2 Hz, H-1β), 6.18 (s, H-1α), 5.63–5.13 (m, 2 H, H-2, 3), 4.37–4.09 (m, 1 H, H-4), 3.35–3.25 (m, 2 H, H-5a,b), 2.10–2.02 (m, 9 H, Ac × 3).

A solution of **33** (0.631 g) in 80% aq AcOH (6.3 mL) was stirred for 70 min at 65 °C. To the cooled solution was added water (6.3 mL), and the precipitate was filtered off. The filtrate was saturated with NaCl, extracted with $CHCl_3$, washed with satd aq $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated to give syrupy 1,2,3-tri-*O*-acetyl-D-arabinofuranose (**34**, 0.222 g, 66%); ^{1}H NMR ($CDCl_3$) δ 6.36–6.30 (m, H-1β), 6.14 (s, H-1α), 5.38–5.32 (m, H-2β, 3β), 5.25–5.04 (m, H-2α, 3α), 4.30–3.93 (m, 1 H, H-4), 3.84–3.77 (m, 2 H, H-5a,b), 2.12–2.07 (m, 9 H, Ac × 3).

A solution of **34** (0.222 g) and *p*-toluenesulfonyl chloride (0.303 g) in pyridine (1.7 mL) was stirred for 8 h at room temperature. The solution was diluted with $CHCl_3$, washed with satd aq $NaHCO_3$, M HCl, and water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (3:2 hexane–EtOAc) to give syrupy 1,2,3-tri-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-D-arabinofuranose (**35**, 0.244 g, 71%); ^{1}H NMR ($CDCl_3$) δ 7.80–7.72, 7.36–7.27 (m, 4 H, Ts-Ar), 6.33–6.27 (m, H-1β), 6.18 (s, H-1α), 5.31–5.26 (m, H-2β, 3β), 5.24–4.94 (m, H-2α, 3α), 4.38–4.11 (m, 3 H, H-4, 5a, b), 2.45 (s, 3 H, Ts-Me), 2.10–2.05 (m, 9 H, Ac × 3).

A mixture of **35** (5.20 g) and KSAc (2.08 g) in DMF (47 mL) was stirred for 2 h at 70 °C. The cooled solution was poured into 2:1 (v/v) EtOAc–water (360 mL), washed 4 times with water (120 mL), dried ($MgSO_4$), and concentrated to give syrupy 1,2,3-tri-*O*-acetyl-5-*S*-acetyl-5-thio-D-arabinofuranose (**36**, 13.68 g, 91%); α anomer: ^{1}H NMR ($CDCl_3$) δ 6.15 (s, H-1), 5.18 (d, $J_{2,3}$ 1.5 Hz, H-2), 4.99 (dd, $J_{3,4}$ 5.0 Hz, H-3), 4.31 (dt, $J_{4,5a}$ 5.3, $J_{4,5b}$ 8.2 Hz, H-4), 3.36 (dd, $J_{5a,5b}$ 14.2 Hz, H-5a), 3.17 (dd, H-5b), 2.36 (s, SAc), 2.14, 2.13, 2.10 (each s, OAc × 3); ^{13}C NMR ($CDCl_3$) δ 169.5,

169.3 (OC=O), 99.2 (C-1), 80.8 (C-2), 78.3 (C-3), 82.7 (C-4), 30.9 (C-5); β anomer: ^{1}H NMR ($CDCl_3$) δ 6.35 (d, $J_{1,2}$ 4.3 Hz, H-1), 5.30 (dd, $J_{2,3}$ 6.6 Hz, H-2), 5.34 (dd, $J_{3,4}$ 4.6 Hz, H-3), 4.09 (dt, $J_{4,5a}$ 5.3, $J_{4,5b}$ 8.2 Hz, H-4), 3.39 (dd, $J_{5a,5b}$ 13.9 Hz, H-5a), 3.19 (dd, H-5b), 2.35 (s, SAc), 2.13, 2.11, 2.08 (each s, OAc × 3); ^{13}C NMR ($CDCl_3$) δ 169.5, 169.3 (OC=O), 93.8 (C-1), 75.5 (C-2), 76.9 (C-3), 80.6 (C-4), 32.9 (C-5), 30.5 (SAc), 21.1, 21.0, 20.8, 20.7, 20.7, 20.4 (OAc).

A solution of **36** (3.37 g) in 0.1 M methanolic NaOMe (40 mL) was stirred for 15 min at room temperature and then neutralized with Dowex 50W-X8 (H^+). The resin was filtered off, and the filtrate was concentrated. The residue was recrystallized from MeOH to give 5-thio-D-arabinopyranose (**37**, 1.03 g, 61%); mp 173–175 °C (from MeOH), lit. [10] mp 172–175 °C (from EtOH); Anal. Calcd for $C_5H_{10}O_4S$: C, 36.13; H, 6.06. Found: C, 36.08; H,6.40.

Acetylation of **37** with Ac_2O in pyridine gave crystalline 1,2,3,4-tetra-*O*-acetyl-5-thio-β-D-arabinopyranose (**38**); mp 119–122 °C (from EtOH); $[\alpha]_D^{26}$ −303° (*c* 1.1, $CHCl_3$); lit. [10] mp 118–120 °C (from EtOH); $[\alpha]_D$ −308° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.14 (dd, 1 H, $J_{1,2}$ 3.0, $J_{1,5b}$ 1.6 Hz, H-1), 5.54 (ddd, 1 H, $J_{4,5a}$ 1.3, $J_{4,5b}$ 4.3 Hz, H-4), 5.52 (dd, 1 H, $J_{2,3}$ 10.7 Hz, H-2), 5.30 (dd, 1 H, $J_{3,4}$ 3.1 Hz, H-3), 3.29 (dd, 1 H, $J_{5a,5b}$ 14.8 Hz, H-5a), 2.75 (ddd, 1 H, H-5b), 2.18, 2.17, 2.03, 2.01 (each s, 3 H × 4, Ac × 4); ^{13}C NMR ($CDCl_3$) δ 170.4, 170.0, 169.9, 169.3 (C=O), 71.9 (C-1), 69.6, 69.0 (C-2, 4), 68.3 (C-3), 27.8 (C-5), 21.0, 20.7, 20.6 (Ac); Anal. Calcd for $C_{13}H_{18}O_8S$: C, 46.70; H, 5.43; S, 9.59. Found: C, 46.46; H, 5.37; S, 9.78.

Inhibition assay.—A solution containing *p*-nitrophenyl α-L-fucopyranoside (0.67 mM, 0.25 mM, 0.10 mM), bovine kidney α-L-fucosidase, and compound **37** (2.0 mM, 1.0 mM, 0.5 mM) in 20 mM sodium citrate buffer, (pH 5.5, 300 μL) was incubated for 30 or 40 min at 25 °C. The reaction was quenched with cooling in an ice bath and by adding glycine buffer (pH 10.0, 500 μL), and the amount of *p*-nitrophenol was measured by its absorbance at 400 nm.

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