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Syntheses of L-Fucopyranose and Its Homologs with Ring Heteroatoms Other than Oxygen. Stereocontrolled Conversion of a Common D-Arabinofuranoside Intermediate

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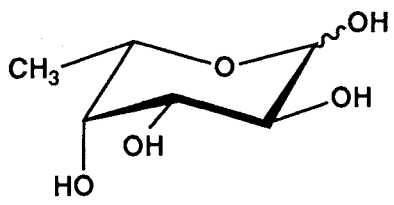
L-Fucopyranose and a couple of L-fucosidase inhibitors, 5-deoxy-5-thio-L-fucopyranose and 1,5-dideoxy-1,5-imino-L-fucitol, were prepared from a common pentose intermediate with α-D-*arabino* configuration. Stereoselectivities on carbon chain elongation of the key intermediate were successfully controlled by choosing the appropriate organometallic reagents.

The widespread occurrence of L-fucopyranose (**1**) in many animal glycolipids and glycoproteins as well as bacterial and plant glycosides etc. suggests diverse biological functions and importance of this sugar. The L-fucose content of animal glycans is known to change under pathological conditions like cancer.[1] Interests derived from these facts have prompted designing and synthesizing several L-fucosidase inhibitors.[2] Thus, Hashimoto et al.[2a] disclosed the potent inhibitory activity of 5-deoxy-5-thio-L-fucopyranose (**2**) by the synthetic methodology. Also, 1,5-dideoxy-1,5-imino-L-fucitol (1-deoxyfuconojirimycin) (**3**), one of the well-known type of inhibitors, has been prepared through many approaches.[2b-2d]

In this communication, we wish to describe the highly stereocontrolled synthesis of **1**, **2**, and **3** through a common key intermediate. The starting material employed was readily accessible methyl α-D-arabinofuranoside tribenzoate (**4**).[3] Our synthetic strategy directed towards **1**, **2**, and **3** included stereocontrolled elongation by one carbon unit at the C-5 position of the key intermediate, methyl 2,3-bis-*O*-*tert*-butyl dimethylsilyl-α-D-*arabino*-pentodialdofuranoside-(1,4) (**6**). Conversion of **4** into **6**



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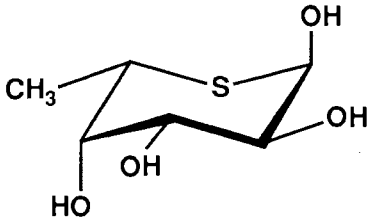

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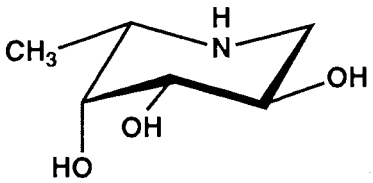

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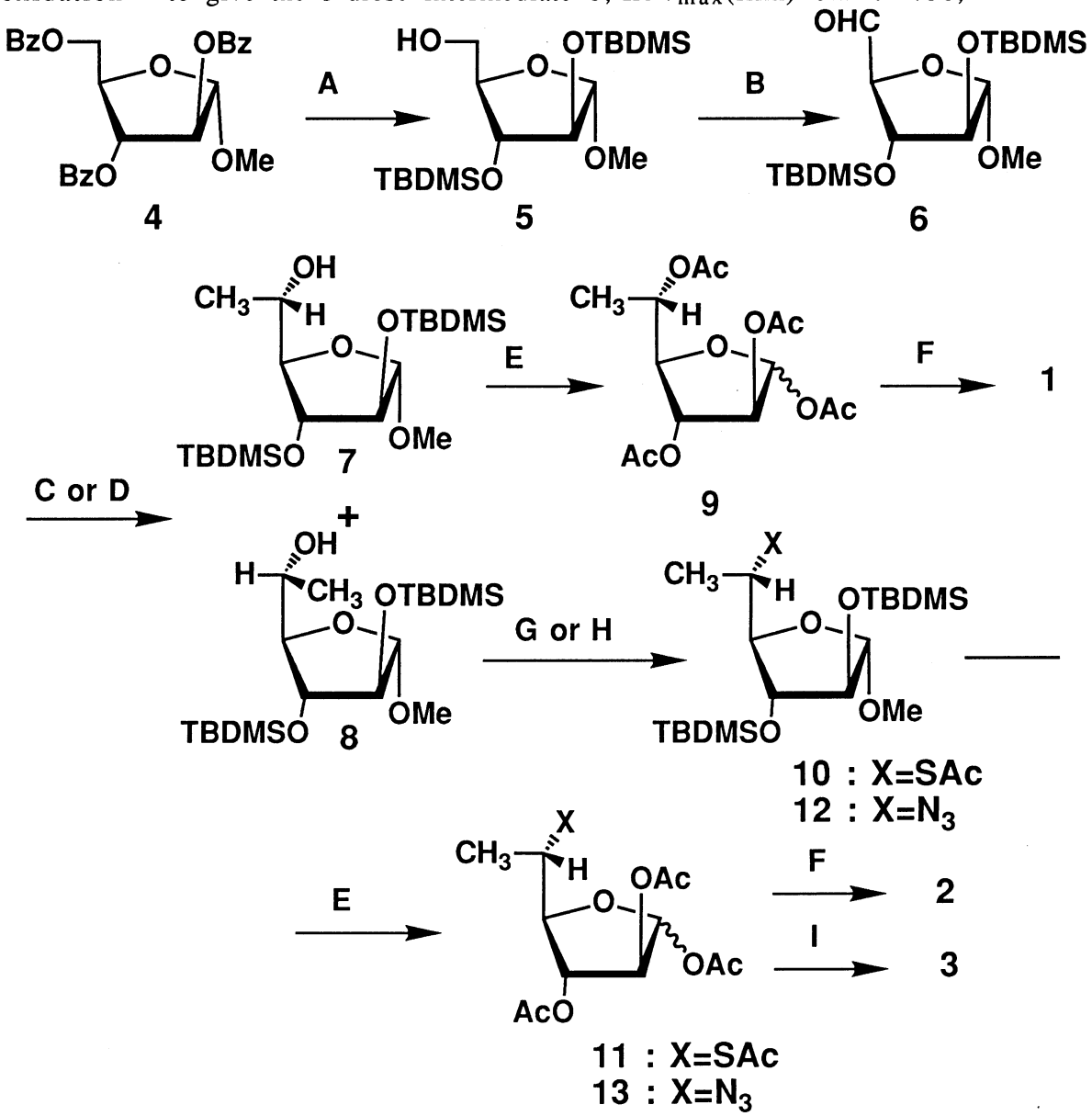
was conducted as shown in the following. After removal of the benzoyl groups of **4**, the resulting triol was transformed into the partially silylated derivative **5**, $[\alpha]_D^{22}$ +46°,[4] in such three steps as selective mono pivaloylation → silylation → reductive depivaloylation (53% yield from **4**). The compound **5** was subjected to Swern oxidation[5] to give the 5-ulose intermediate **6**, IR ν_{max}(film) cm^{-1}: 1730, in



Reagents: (A) 1) NaOMe, MeOH, 2) pivaloyl chloride (1.3 equiv.), pyridine, 3) TBDMSCl, imidazole, DMF, 4) $LiAlH_4$, ether (53% from **4**); (B) oxalyl chloride, DMSO, CH_2Cl_2, -70 °C and then Et_3N; (C) Me_2CuLi, ether, -78 °C (70% from **5**); (D) Me_3Al, hexane, -78 °C (70% from **5**); (E) Ac_2O, AcOH, conc. H_2SO_4 (15:15:1) (quant.); (F) NaOMe, MeOH; (G) 1) p-TsCl, pyridine, 2) KSAc, HMPA, 85 °C (74% from **8**); (H) 1) MsCl, pyridine, 2) NaN_3, DMSO, 80 °C (84% from **8**); (I) 1) NaOMe, MeOH, 2) 10% Pd-C, MeOH (81% from **12**).

quantitative yield, which was used for the next step without thorough purification.

As we expected to introduce heteroatoms other than oxygen by S_N2 displacement of the 5-sulfonyloxy group of a 6-deoxy-hexose precursor, we needed both diastereomers of 6-deoxy-5-hydroxyl hexose derivatives like **7** and **8** with reversed configurations at C-5 for preparations directed towards **1** and **2**, **3**. Attainment of efficient diastereofacial selective addition of a methyl unit to carbonyl group of **6** was the most tough problem to be solved. Taking the presence of many oxygenated functionalities in the substrate into account, we searched suitable methyl organometallic reagents for conversion of **6** into **7** or **8**. As shown in Table 1, the ratio of produced **7** and **8** varied in wide range depending on the kind of the reagent employed, whereas chemical yields were in narrow range in all entries and moderately good. Reaction of **6** with Me_2CuLi in ether[6] gave **7**, $[\alpha]_D^{22}$ +47°; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.27 (3H, d, J=6.7 Hz, Me), 4.71 (1H, brs, C-1), in high diastereofacial selectivity, while use of Me_3Al in hexane[7] resulted in predominant production of the diastereomer **8**, $[\alpha]_D^{22}$ +29°; ^{1}H-NMR δ: 1.21 (3H, d, J= 6.7 Hz, Me), 4.73 (1H, brs, C-1). These isomers (**7** and **8**) could be separated by silica-gel column chromatography, and their configurations were later confirmed by conversion into the known compounds (**1**- **3**) (vide infra). Although explanation about the marked difference of the diastereofacial selectivities between Me_2CuLi and Me_3Al might be interesting, the highly oxygenated functionality and the presence of the bulky protecting groups in the substrate interfered simple rationalization of the mechanism. Very recently, Hashimoto et al.[8] also reported a stereoselctive addition using Me_3Al in a similar system.

After achievement of the efficient syntheses of **7** and **8**, these diastereomers were further converted into **1** and **2**, **3**, respectively. For preparation of **1**, compound

Table 1. Diastereomeric Ratios from the Reaction of Aldehyde **6** with Methyl Nucleophiles

Entry	Reagent	Solvent	Temp/°C	Ratio (**7**/**8**)[a]	Yield/%
1	MeMgBr	THF	0	62 / 38	84
2	MeMgI	ether	-20	71 / 29	76
3	Me_2CuLi	ether	-78	92 / 8	70
4	(*i*-PrO)$_3$TiMe	ether	-42	47 / 53	50
5	MeLi	hexane	-78	33 / 67	66
6	$MeCeCl_2$	THF	-78	25 / 75	88
7	MeLi	ether	-110	24 / 76	76
8	Me_3Al	hexane	-78	4 / 96	70

a) Ratios were determined by 500 MHz NMR.

7 was subjected to acetolysis (Ac_2O - AcOH - conc. H_2SO_4 (15:15:1), 0 °C - rt) to give tetraacetate **9**, IR ν_{max}(film) cm^{-1}: 1750, in almost quantitative yield. Finally, **9** was de-*O*-acetylated with NaOMe in MeOH to give L-fucose (**1**), $[\alpha]_D^{21}$ -73° (H_2O, equilibrium), which was identical with an authentic sample (Fluka AG, Buchs), $[\alpha]_D^{21}$ -74° (H_2O, equilibrium), except the anomeric ratios. On the other hand, for synthesis of **2**, compound **8** was reacted with p-TsCl in pyridine to give the 5-tosylate, which was treated with potassium thioacetate in HMPA at 85 °C, giving thioacetate **10**, $[\alpha]_D^{25}$ +27°; ^{1}H-NMR δ: 2.33 (SAc), in 73% yield from **8**. Thioacetate **10** was subjected to acetolysis to provide tetraacetate **11**, IR ν_{max}(film) cm^{-1}: 1740, 1696, in almost quantitative yield. The acetyl group of **11** was removed with base to give 5-deoxy-5-thio-L-fucose (**2**), mp 152 °C; $[\alpha]_D^{22}$ -227° (H_2O, equilibrium), (lit[2a]: mp 160 °C, $[\alpha]_D^{25}$ -230° (H_2O, equilibrium)). In a similar way, **8** was reacted with MsCl in pyridine to convert into the 5-mesylate, which was reacted with NaN_3 in DMSO at 80 °C to afford the azido derivative **12**, $[\alpha]_D^{25}$ +85°; IR ν_{max}(film) cm^{-1}: 2111, in 84% yield from **8**. Acetolysis of **12** resulted in triacetate **13**, IR ν_{max}(film) cm^{-1}: 2116, 1750. After removal of all acetyl groups of **13** with base, the resulting compound was hydrogenated over 10% Pd-C under H_2 atmosphere to give 1,5-dideoxy-1,5-imino-L-fucitol (**3**), $[\alpha]_D^{25}$ -48° (H_2O), (lit: $[\alpha]_D^{20}$ -49°,[2b] -47° [2c] (H_2O)).

In conclusion, combination of the well-protected pentodialdofuranoside derivative **6** and suitable organometallic reagents resulted in efficient selective formation of two diastereoisomers with L-*galacto* and D-*altro* configurations. These selectivities will also be of wide applicability besides the preparation of **1**, **2**, and **3**.

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