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A New Synthesis of α-L-Fucose

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A new synthesis of α-L-fucose from D-glucose is described. The key intermediate is methyl 2,3-di-O-acetyl-4,6-O-benzylidene-α-D-altropyranoside (1), synthesized from methyl α-D-glucopyranoside by known procedures. Compound 1 was converted into methyl 2,3-di-O-acetyl-4-O-benzoyl-6-bromo-6-deoxy-α-D-altropyranoside (2) by treatment with N-bromosuccinimide. Dehydrobromination of 2 afforded the 5,6-unsaturated glycoside (4), which underwent reduction by hydrogen, mainly with inversion at C-5, to give methyl 2,3-di-O-acetyl-4-O-benzoyl-6-deoxy-β-L-galactopyranoside (5) with a small amount of the isomeric methyl 2,3-di-O-acetyl-4-O-benzoyl-6-deoxy-α-D-altropyranoside (3). The ratio of 3 to 5 was about 1 to 4.

Deacylation of a mixture of 3 and 5 gave crystalline methyl β-L-fucopyranoside (6) and a syrupy methyl 6-deoxy-α-D-altropyranoside. Acidic hydrolysis of 6 afforded crystalline α-L-fucose in 19.3% yield from 1 *via* 5 steps.

Keywords——L-fucose synthesis from D-glucose; methyl altropyranoside derivatives; methyl 6-deoxy-altropyranoside derivatives; 5,6-unsaturated altropyranoside; catalytic hydrogenation with inversion; NBS

In 1954, Akiya and Suzuki reported an ingenious synthetic route to L-fucose from D-galactose, but the yield was low.[2] Recently, Dejter-Juszynski and Flowers[3] synthesized the sugar from D-galactose *via* five steps in 15% yield. This paper reports a new synthetic route to α-L-fucose from D-glucose.

The key intermediate of our route is methyl 2,3-di-O-acetyl-4,6-O-benzylidene-α-D-altropyranoside (**1**), which is easily synthesized from D-glucose.[4] Our method consists of the introduction of a double bond between the C-5 and C-6 positions in **1**, and dehydroxylation at the C-6 position with concomitant isomerization of the C-5 position by catalytic hydrogenation of the double bond. The advantage of our route is that α-L-fucose is synthesized without the use of the unpleasant mercaptan, and the triple column chromatography used in Flowers' procedure is not required. α-L-Fucose is obtained in 19.3% yield from **1** *via* five steps.

Refluxing a mixture of **1**,[4b] N-bromosuccinimide, and barium carbonate in carbon tetrachloride and 1,2-dichloroethane afforded crystalline methyl 2,3-di-O-acetyl-4-O-benzoyl-6-bromo-6-deoxy-α-D-altropyranoside (**2**) in 72% yield. Catalytic reduction of **2** over a Raney nickel catalyst in the presence of pyridine gave methyl 2,3-di-O-acetyl-4-O-benzoyl-6-deoxy-α-D-altropyranoside (**3**) as a syrup in 74.7% yield.

A mixture of **2** and silver fluoride in dry pyridine was stirred to yield methyl 2,3-di-O-acetyl-4-O-benzoyl-α-D-*arabino*-hex-5-enopyranoside (**4**) as a syrup in 70.9% yield.

A solution of **4** in methanol was hydrogenated over palladium black. After hydrogenation, thin-layer chromatography (TLC) indicated the presence of two products, *Rf* 0.59 (minor) and 0.49 (major), which were isolated by column chromatography. The minor product was eluted first and isolated as a syrup in 17.2% yield, indistinguishable from **3** by

1) Location: *Tanabe-dori, Mizuho-ku, Nagoya, 467, Japan.*
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TLC and infrared (IR) spectrum. Further elution with the same solvent eluted the major product, which was isolated as colorless prisms in 75.3% yield. The product had the same elemental composition as **3** and the nuclear magnetic resonance (NMR) spectral data (Table I) were consistent with the assigned structure of methyl 2,3-di-O-acetyl-4-O-benzoyl-6-deoxy-β-L-galactopyranoside (**5**).

In the NMR spectra of **3** and **5**, the anomeric methoxyl groups appeared respectively at δ 3.43 and 3.58 ppm as a three-proton singlet (Table I). From the ratio of the intensities, the hydrogenation product of **4** was found to be a mixture of **3** (20%) and **5** (80%). This is reasonably consistent with the ratio calculated from the amounts of the isolated products.

Table I. NMR Spectra of Compounds **2**—**5** in Chloroform-d

Compound	Chemical shifts (δ)[a] (first-order coupling, Hz, in parentheses)									
	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6 ($J_{5,6'}$)	H-6′ ($J_{6,6'}$)	Aryl	OMe	Ac
2	4.69s	←5.48—4.99m→			4.48m	3.76—3.32m		8.08—7.94m 7.64—7.20m	3.47s	2.14s, 2.07s
3	4.62s	←5.40—4.95m→			4.36m (6.5)	←1.31d→		8.16—7.88m 7.68—7.28m	3.43s	2.14s, 2.07s
4	4.63d (5)	5.36dd (9)	5.19dd (3.5)	5.94d	—	4.90d	4.81d (1)	8.20—7.90m 7.70—7.20m	3.57s	2.11s, 2.01s
5	4.46d (7)	5.30dd (10)	5.17dd (3)	5.52dd (1)	3.94oct (6.5)	←1.29d→		8.30—8.00m 7.72—7.30m	3.58s	2.07s, 1.95s

a) Signal multiplicities: d, doublet; dd, double doublet; m, multiplet; oct, octet; s, singlet.

We reported previously that catalytic hydrogenation of the exocyclic double bond in lactose-5-ene heptaacetate gave predominantly the 6-deoxy-L-ido isomer rather than the 6-deoxy-D-gluco isomer.[5] In compound **4**, a bulky benzoyl group is present below the 6-deoxy-D-altropyranose ring. Thus, predominant formation of **5** over **3** may be interpreted in terms of a similar structural correlation of **4** with lactose-5-ene heptaacetate.

Deacylation of **5** gave methyl 6-deoxy-β-L-galactopyranoside (methyl β-L-fucopyranoside) (**6**), mp 124—125°, $[\alpha]_D^{24}$ +17°. However, methyl 6-deoxy-α-D-altropyranoside, the deacylation product of **3**, is a syrup.[6] Thus, after hydrogenation of **4**, the mixture was deacylated without separation of **3** and **5**; crystalline **6** can be isolated from the isomeric methyl 6-deoxy-α-D-altropyranoside.

Acidic hydrolysis of **6** gave α-L-fucose (**7**) in 60.1% yield. The product was crystallized from ethanol and gave a crystalline methylphenylhydrazone (**8**).[7]

Experimental

Melting points are uncorrected. Solutions were evaporated down in a rotary evaporator below 40° under a vacuum. Instruments used were the same as before.[5] TLC on Kieselgel GF_{254} (5×20 cm) (E. Merck, Darmstadt, Germany) was performed with the following solvent combinations (v/v): (A), $CHCl_3$–acetone (6:1); (B), benzene–ether (10:1, two developments); (C), cyclohexane–ether (1:3); (D), 70% 2-PrOH–AcOEt (2:1).

Methyl 2,3-Di-O-acetyl-4-O-benzoyl-6-bromo-6-deoxy-α-D-altropyranoside (**2**)——N-Bromosuccinimide (5.8 g, 32.6 mmol) and $BaCO_3$ (6.5 g, 32.9 mmol) were added to a suspension of **1**[4b] (10 g, 27.3 mmol) in CCl_4 (145 ml) and 1,2-dichloromethane (50 ml). The mixture was refluxed with efficient stirring for 3 hr, then filtered, and the filtrate was evaporated to dryness. The residue was dissolved in ether, washed with a small volume of H_2O to remove succinimide, dried over $CaCl_2$, and evaporated to a syrup, which gave two spots, *Rf* 0.89 (major) and 0.56 (minor), on TLC (solvent A). The syrup was crystallized from EtOH and the cry-

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stals were recrystallized from AcOEt to afford **2** as colorless needles (8.8 g, 72%), mp 122—123°, $[\alpha]_D^{25}$ +46.7° (c=1.07, $CHCl_3$). TLC: *Rf* 0.89 (solvent A), 0.59 (B), 0.59 (C). *Anal.* Calcd. for $C_{18}H_{21}BrO_8$: C, 48.56; H, 4.75. Found: C, 48.30; H, 5.04.

Methyl 2,3-Di-O-acetyl-4-O-benzoyl-6-deoxy-α-D-altropyranoside (3)——A solution of **2** (1.5 g) in MeOH (20 ml) containing pyridine (1 ml) was hydrogenated over a Raney Ni catalyst at room temperature under atmospheric pressure. Removal of the catalyst and solvent gave a syrup, which was dissolved in CH_2Cl_2 (50 ml), washed successively with 1 M HCl, aq. $NaHCO_3$, and H_2O, dried over $CaCl_2$, and then concentrated to a syrup. A solution of the syrup in CH_2Cl_2 (2 ml) was chromatographed on a column of silica gel, eluting with benzene–ether (20: 1). Removal of the solvent from the fractions having *Rf* 0.88 (solvent A) afforded a syrup (919 mg, 74.7%), $[\alpha]_D^{27}$ +44.4° (c=1.44, $CHCl_3$). TLC: *Rf* 0.88 (solvent A), 0.55 (B), 0.59 (C). *Anal.* Calcd. for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 58.66; H, 5.99.

Methyl 2,3-Di-O-acetyl-4-O-benzoyl-α-D-arabino-hex-5-eno-pyranoside (4)——Dry silver fluoride (2.28 g, 18 mmol) was added to a solution of **2** (4 g, 9 mmol) in dry pyridine (40 ml), and the suspension was shaken, with the exclusion of light, at room temperature for 22 hr. The mixture was then diluted with CH_2Cl_2 (100 ml), poured into ice-H_2O (300 ml) and filtered. The organic layer was washed successively with 5% H_2SO_4, aq. $NaHCO_3$, and H_2O, and then dried over $CaCl_2$. Removal of the solvent gave **3** (2.32 g, 70.9%) as a syrup. $[\alpha]_D^{21}$ +0.5° (c=0.78, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1663 (C=C). TLC: *Rf* 0.89 (solvent A), 0.67 (B), 0.59 (C). *Anal.* Calcd. for $C_{18}H_{20}O_8$: C, 59.34; H, 5.53. Found: C, 59.48; H, 5.52.

Methyl 2,3-Di-O-acetyl-4-O-benzoyl-6-deoxy-β-L-galactopyranoside (Methyl 2,3-Di-O-acetyl-4-O-benzoyl-β-L-fucopyranoside) (5)——A solution of **4** (3 g) in MeOH (60 ml) was added to a suspension of Pd black in MeOH prepared from $PdCl_2$ (1 g) in MeOH.[8] After the theoretical amount of H_2 had been absorbed, the catalyst and solvent were removed to afford a syrup, which gave two spots, *Rf* 0.59 (minor) and 0.49 (major) on TLC (solvent C). The syrup was dissolved in CH_2Cl_2 (2 ml) and chromatographed on a column of silica gel, eluting with cyclohexane–ether (1: 1). Removal of the solvent from the faster moving fraction gave a syrup (0.52 g, 17.2%), which was identified as **3**.

Further elution of the column with the same solvent eluted **5**. Removal of the solvent gave an amorphous powder which was crystallized from ligroin. Recrystallization from ligroin gave **5** as colorless prisms (2.27 g, 75.3%), mp 92—93°, $[\alpha]_D^{20}$ −74° (c=1.17, $CHCl_3$). TLC: *Rf* 0.85 (solvent A), 0.57 (B), 0.49 (C). *Anal.* Calcd. for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 59.16; H, 6.03.

Methyl 6-Deoxy-β-L-galactopyranoside (Methyl β-L-Fucopyranoside) (6)——1) From Compound **5**: Methanolic NaOMe (0.5 M, 1 ml) was added to a solution of **5** (2 g) in dry MeOH (30 ml) at room temperature with stirring. The mixture was stirred for 1 hr. After neutralization with dry Amberlite IR-120 (H^+) resin, the resin and solvent were removed to give a syrup, which was washed with petr. ether (30 ml) to remove methyl benzoate. The residue was dissolved in ether and kept at 5° to crystallize. Recrystallization from ether gave **6** as colorless needles (836 mg, 85.9%), mp 124—125°, $[\alpha]_D^{24}$ +17° (c=1.09, H_2O). [lit.[9] mp 123°, $[\alpha]_D^{20}$ +15° (c=1, H_2O)]. TLC: *Rf* 0.64 (solvent D).

2) From the Hydrogenation Product of **4**: Methanolic NaOMe (0.5 M, 1.5 ml) was added to a solution of a mixture of **3** and **5**, obtained by reduction of **4** (3 g), in dry MeOH (45 ml). The mixture was stirred at room temperature for 3 hr and then treated as described in 1) to afford colorless needles (926 mg, 63.1%). The product was indistinguishable from the product prepared by method 1).

6-Deoxy-α-L-galactose (α-L-Fucose) (7)——A mixture of **6** (500 mg) and 0.5 M H_2SO_4 (10 ml) was heated at 98° for 2 hr. After neutralization with $BaCO_3$, it was filtered, treated with charcoal, and evaporated to a thin syrup, which was dissolved in EtOH and kept at 5° to crystallize. Recrystallization from EtOH yielded **7** as colorless prisms (277 mg, 60.1%), mp 139—140°, $[\alpha]_D^{22}$ −76.1° (equilibrium, c=0.65, H_2O). [lit.[3] mp 137—139°, $[\alpha]_D^{23}$ −75° (equilibrium, c=0.8, H_2O; lit.[7] mp 140—141°, $[\alpha]_D^{17}$ −76° (equilibrium, c=2, H_2O)]. TLC: *Rf* 0.59 (solvent D).

L-Fucose Methylphenylhydrazone (8)——1-Methyl-1-phenylhydrazine (0.1 ml, 0.85 mmol) was added to a solution of **7** (50 mg, 0.30 mmol) in H_2O (0.8 ml), EtOH (0.8 ml), and glacial AcOH (2 drops). The mixture was kept at 5° for 2 days. The resulting crystals were collected by filtration, washed with a small volume of EtOH and ether, then dried at 100° for 30 min The crystals (72.6 mg, 88.9%) had mp 184—185°, $[\alpha]_D^{22}$ +6.1° (c=1.01, pyridine). [lit.[3] mp 180—182°, $[\alpha]_D^{23}$ +6° (c=5, pyridine); lit.[7] mp 172—173°, $[\alpha]_D$ +5° (c=4, pyridine)].

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