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Stereoselective and Rapid Synthesis of D-Mannose

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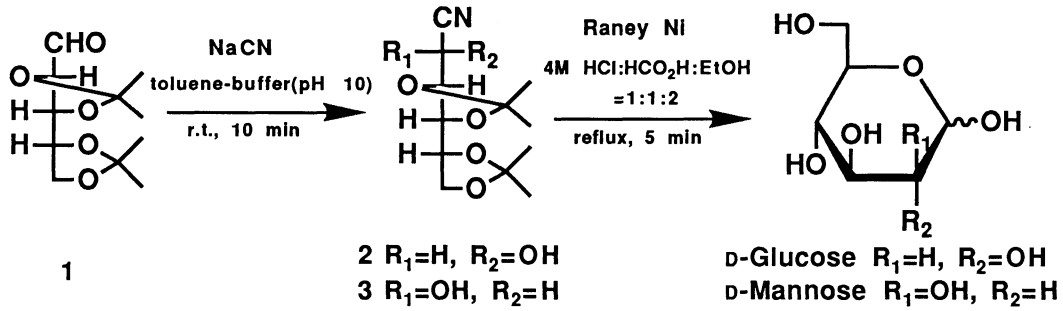
During the course of our studies on labeling reactions with tracer elements, a new rapid and stereoselective synthesis of D-mannose was found. Reaction of 2,3:4,5-di-*O*-isopropylidene-D-arabinose with trimethylsilylcyanide and zinc iodide in dichloromethane followed by reduction gave D-mannose in good yield.

Studies of the brain function utilizing positron emission tomography (PET) have yielded a greater understanding of senility, which is becoming an increasingly important medical and social issue with our aging society.[1] However carbon-11 labeled compounds needed for PET studies have half-lives of only 20 minutes, and their synthesis must be accomplished in a few minutes. Furthermore, the synthetic scale should be very small and the concentration of labeling agent is always less than micro molar. D-[^{11}C]Glucose has been prepared from $^{11}CO_2$ by photosynthesis[2] using spinach or by chemical synthesis[3] using the Kiliani-Fischer method. However, photosynthesis gives many kinds of byproducts and the stereochemical yield of the Kiliani-Fischer reaction is low due to the equilibrium between the starting material and cyanohydrin derivative. For example, reaction of D-arabinose with NaCN, followed by reductive hydrolysis with Ni/Al in 30% formic acid gives a mixture of D-glucose and D-mannose.[3] Thus, a new stereoselective and rapid reaction for labeled sugars is highly desirable. This paper deals with a stereoselective and rapid synthesis of D-mannose which can be adapted to a labeling reaction.

As shown in Scheme 1, the reaction of 2,3:4,5-di-*O*-isopropylidene-D-arabinose (**1**)[4] (20 mg, 87 μmol) with NaCN (4.3 mg, 87 μmol) in a mixture of 1M Na_2CO_3-HCl buffer (pH 10, 400 μl) and toluene (400 μl) proceeded quickly to give a mixture of D-gluconononitrile **2**[5] and D-mannonitrile **3**[6] in the ratio of 2.2 to 1. The reductive hydrolysis of the mixture with Raney nickel (40 mg)[7,8] gave a mixture of D-glucose and D-mannose in 44% yield (D-glucose:D-mannose=1.9:1) from **1**. The mechanism is unknown but it seems that the



Scheme 1.

stereoselectivity is brought about by reaction occurring at the boundary of the two-phases under the steric influence of the protecting groups.

Although the cyanohydrins **2** and **3** could be separated by silicagel column chromatography, racemization was found to occur in solution. Since the trimethylsilylation of the hydroxy group in D-arabinose might prevent racemization and the bulkiness of the trimethylsilyl group might be effective for stereoselective control, a rapid preparation of trimethylsilyl cyanide (TMSCN) and a rapid reaction of it with **1** in the presence of Lewis acids was studied. It was found that the reaction of trimethylsilyl chloride with polymer-supported NaCN in *N*-methyl-2-pyrrolidinone proceeded quantitatively within 3 minutes using a modification of Sukata's method,[9] and TMSCN could be easily isolated by distillation. By modifying the procedures in the literature[10,11] the effectiveness of some common Lewis acid catalysts for the reaction of **1** with TMSCN was investigated as shown in Table 1.

Table 1. Yields of D-Mannose from Compound **1** [a]

Entry No.	Lewis acid	Yield / mg (%) [b]		
		D-Mannose	D-Glucose	D-Arabinose [c]
1	Et_2AlCl	7.5 (47.9)	—	3.0 (23.0)
2	BF_3-Et_2O	10.8 (68.9)	—	—
3	$SnCl_4$	11.3 (72.2)	—	2.3 (17.7)
4	$TiCl_4$	2.2 (14.0)	—	2.3 (17.7)

a) General conditions: i) Compound **1** (20 mg, 87 μmol), TMSCN (37 μl, 3.2 equiv.), Lewis acid (1.1 equiv.), CH_2Cl_2 (500 μl), -40 °C, 2 h, ii) Raney nickel (40 mg), HCO_2H:4 M HCl = 1:1 (1.0 ml), EtOH (1.0 ml), reflux 5 min.
b) Determined by HPLC analysis.
c) Compound **1** was recovered as D-arabinose.

Although excellent stereoselectivity for D-mannose was observed the reactions were too slow to be useful for carbon-11 labeling. Attempts to increase the rate by increasing the reaction temperature failed due to

cleavage of the isopropylidene protecting groups of **1** under the influence of the Lewis acids. In light of these results we selected some milder Lewis acids for reaction at room temperature (Table 2).

The reaction was catalyst-dependant; the rate decreasing in the order of ZnI_2, $ZnBr_2$, CuCN, $ZnCl_2$, and $MgBr_2$, and in all cases D-mannose was preferentially produced rather than D-glucose. Table 2, entries 1-6 show that CH_2Cl_2 was the most suitable solvent for the cyanation with TMSCN in the presence of ZnI_2. The reaction of **1** with TMSCN/ZnI_2 proceeded within 3 minutes, and the resulting intermediate **4** was converted to D-mannose in 86.3% yield (entry 1)[12] by reductive hydrolysis with Raney nickel. The

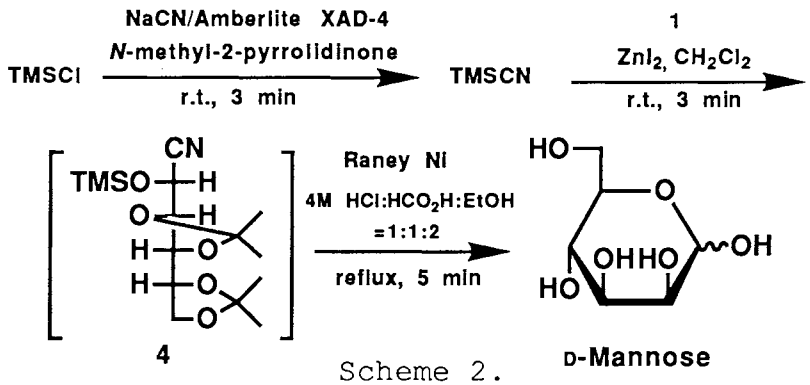
Table 2. Yields of D-Mannose and D-Glucose from Compound **1**[a]

Entry No.	Lewis acid	Solvent	Yield / mg (%)[b]		
			D-Mannose	D-Glucose	D-Arabinose[c]
1	ZnI_2	CH_2Cl_2	13.5 (86.3)	—	—
2	ZnI_2	$CHCl_3$	5.0 (31.9)	—	0.4 (3.1)
3	ZnI_2	CCl_4	1.3 (8.3)	—	11.1 (85.1)
4	ZnI_2	THF	3.7 (23.6)	—	0.7 (5.4)
5	ZnI_2	Et_2O	5.5 (35.1)	—	—
6	ZnI_2	benzene	3.6 (23.0)	—	0.4 (3.1)
7	$ZnBr_2$	CH_2Cl_2	5.8 (37.1)	0.5 (3.2)	3.1 (23.8)
8	$ZnCl_2$	CH_2Cl_2	0.2 (1.3)	—	6.1 (46.8)
9	$MgBr_2$	CH_2Cl_2	—	—	7.4 (56.7)
10	CuCN	CH_2Cl_2	1.0 (6.4)	—	8.9 (68.3)

a) General conditions: i) Compound **1** (20 mg, 87 μmol), TMSCN (37 μl, 3.2 equiv.), Lewis acid (1.1 equiv.), solvent (500 μl), room temperature, 3 min, ii) Raney nickel (40 mg), HCO_2H:4 M HCl = 1:1 (1.0 ml), EtOH (1.0 ml), reflux 5 min.

b) Determined by HPLC analysis.

c) Compound **1** was recovered as D-arabinose.



Scheme 2.

conversion was performed quickly without contamination with byproducts such as D-glucose or D-arabinose derived from unreacted **1**.

The new rapid and stereoselective synthesis is capable of application to both a general synthesis of sugar compounds as well as microsynthesis of labeled sugars.

References

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5) ^{1}H NMR (C_6D_6) δ=1.133 (3H, s, CH_3), 1.286 (3H, s, CH_3), 1.396 (3H, s, CH_3), 1.419 (3H, s, CH_3), 3.672 (1H, m, J=6.0 and 9.1 Hz, H-5), 3.771 (1H, dd, J=3.0 and 9.1 Hz, H-3), 3.878 (1H, dd, J=6.0 and 9.1 Hz, H-6a), 3.982 (1H, q, J=9.1 Hz, H-6b), 4.178 (1H, t, J=9.1 Hz, H-4), 4.461 (1H, d, J=11.3 Hz, 1-OH), 4.633 (1H, dd, J=3.0 and 11.3 Hz, H-2).
6) ^{1}H NMR ($CDCl_3$) δ=1.355 (3H, s, CH_3), 1.431 (3H, s, CH_3), 1.441 (3H, s, CH_3), 1.471 (3H, s, CH_3), 3.763 (1H, dd, J=7.9 and 8.5 Hz, H-4), 4.010 (1H, dd, J=4.3 and 8.4 Hz, H-6a), 4.070 (1H, m, J=4.3, 5.7, and 8.5 Hz, H-5), 4.120 (1H, dd, J=5.1 and 7.9 Hz, H-3), 4.192 (1H, dd, J=5.7 and 8.4 Hz, H-6b), 4.588 (1H, d, J=5.1 Hz, H-2).
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8) Raney nickel was purchased from the Nakalai Tesque, INC., and used without further purification.
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12) The synthetic procedure: To a solution of **1** (20 mg, 87 μmol) in CH_2Cl_2 (500 μl) were added ZnI_2 (31 mg, 97 μmol) and TMSCN (37 μl, 3.2 equiv.) The mixture was stirred for 3 minutes at room temperature and filtered. The filtrate was evaporated in vacuo. To the residue were added EtOH (1.0 ml), formic acid (0.5 ml), 4 M HCl (0.5 ml), and Raney nickel (40 mg). The mixture was refluxed for 5 minutes and filtered. The filtrate was evaporated in vacuo. The residue was purified by preparative HPLC to give D-mannose (11.0 mg, 70%).

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